



A process for prioritising systematic reviews in tinnitus

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Complete List of Authors:	Sereda, Magdalena; University of Nottingham, NIHR Nottingham Biomedical Research Centre, Hearing Sciences, Division of Clinical Neuroscience, School of Medicine McFerran, Don; Essex County Hospital, Otolaryngology; Axon, Emma; University of Nottingham, Cochrane Skin, Centre of Evidence Based Dermatology Baguley, David; University of Nottingham, Hearing Sciences, NIHR Nottingham Biomedical Research Centre, Hearing Sciences, Division of Clinical Neuroscience, School of Medicine Hall, Deborah; University of Nottingham, NIHR Nottingham Biomedical Research Centre, Hearing Sciences, Division of Clinical Neuroscience, School of Medicine; University of Nottingham - Malaysia Campus, Jalan Broga, 43500 Semenyih, Selangor Darul Ehsan Potgieter, Iskra; University of Nottingham, NIHR Nottingham Biomedical Research Centre, Hearing Sciences, Division of Clinical Neuroscience, School of Medicine Cima, Rilana; Adelante, Centre of expertise in Rehabilitation & Audiology; Maastricht University, Clinical Psychological Science Cox, Samantha; University of Oxford, Cochrane ENT, Nuffield Department of Surgery Hoare, Derek; University of Nottingham, NIHR Nottingham Biomedical Research Centre, Hearing Sciences, Division of Clinical Neuroscience, School of Medicine
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Sereda et al. *Prioritising topics for systematic review*

A process for prioritising systematic reviews in tinnitus

Technical report

Magdalena Sereda ^{1,2*}, Don McFerran ³, Emma Axon ⁴, David M Baguley ^{1,2,5}, Deborah A Hall ^{1,2,5,6}, Iskra Potgieter ^{1,2}, Rilana Cima ^{7,8}, Samantha Cox ⁹, Derek J Hoare ^{1,2}

1 National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Ropewalk House, 113 The Ropewalk, Nottingham, UK

2 Hearing Sciences, Division of Clinical Neuroscience, School of Medicine, University of Nottingham, Nottingham, UK

3 East Suffolk and North Essex NHS Foundation Trust, Colchester General Hospital, Turner Road, Colchester, UK

4 Cochrane Skin, Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK

5 Nottingham University Hospitals NHS Trust, Queens Medical Centre, Derby Road, Nottingham, UK

6 University of Nottingham Malaysia, Jalan Broga, 43500 Semenyih, Selangor Darul Ehsan, Malaysia

7 Maastricht University, Department of Clinical Psychological Science, Maastricht, Netherlands

8 Adelante, Centre for Expertise in Rehabilitation & Audiology, Hoensbroek, Limburg, Netherlands

9 Cochrane ENT, Nuffield Department of Surgery, University of Oxford, Oxford, UK

*Corresponding author:

Magdalena Sereda

National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre
Ropewalk House, 113 The Ropewalk

NG1 5DU, Nottingham, UK

Magdalena.Sereda@nottingham.ac.uk

Sereda et al. Prioritising topics for systematic review

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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3 **1 ABSTRACT**

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7
8
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10
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12
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14
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17 scale of work that would be required to conduct these reviews. Secondly, using the pre-
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Cochrane as the systematic review platform. The criteria produced by this process identified
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1 *Sereda et al. Prioritising topics for systematic review*

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INTRODUCTION

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9 26 Systematic reviews and meta-analyses represent the highest level of evidence for the
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11 27 effectiveness of clinical interventions and hold a critical place in informing health policy and
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13 28 evidence-based practice (Greenwell et al.2016; Morata et al., 2017). One of the foremost
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15 29 organisations producing systematic reviews is Cochrane, which is a UK based charity (not-
16
17 30 for-profit organisation) that supervises a global independent network of healthcare
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19 31 practitioners, researchers, patient advocates and others. It represents more than 11,000
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21 32 members and over 68,000 supporters from over 130 countries
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23 33 (<https://www.cochrane.org/about-us>). Cochrane authors conduct systematic reviews of
24
25 34 health-care interventions and diagnostic tests which are published as Cochrane Reviews in
26
27 35 the Cochrane Library. Previously, Cochrane authors self-selected topics for their reviews and
28
29 36 submitted proposals to Cochrane for approval. This process has been updated and now,
30
31 37 Cochrane groups are encouraged to work strategically to respond to the needs of funders and
32
33 38 key stakeholders to produce reviews on topics of the highest priority to users. One approach
34
35 39 to prioritising these reviews is to conduct a scoping exercise ([https://ent.cochrane.org/our-](https://ent.cochrane.org/our-evidence/prioritisation/scoping-projects)
36
37 40 [evidence/prioritisation/scoping-projects](https://ent.cochrane.org/our-evidence/prioritisation/scoping-projects)). Cochrane Ear, Nose, & Throat Disorders (Cochrane
38
39 41 ENT) group this has developed suites of reviews with an “optimal, shared protocol with a
40
41 42 well-designed and consistent set of outcome measures” (Cochrane ENT Group, 2019).
42
43 43 In this report we describe a comprehensive exercise used to prioritise systematic reviews of
44
45 44 interventions for tinnitus conducted for the Cochrane ENT group.

46
47 45 Subjective tinnitus is described as the perception of sound in the absence of an external sound
48
49 46 source (Jastreboff and Hazell, 2004). It is a symptom experienced by 10-30% of the adult
50
51 47 population (McCormack et al., 2016). About 20% of people with tinnitus experience it as
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1 *Sereda et al. Prioritising topics for systematic review*

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3 48 bothersome (McCormack et al., 2016). Problems associated with tinnitus include sleep
4
5 49 disturbances, hearing difficulties, difficulties with concentration, social isolation, anxiety,
6
7 50 depression, and emotional difficulties such as irritation or stress (Davis and El Refaie, 2000).
8
9 51 It is estimated that the prevalence of tinnitus in those adults seeking medical help for hearing
10
11 52 problems is as high as 85% (Axelsson and Ringdahl, 1989; Davis and El Refaie, 2000;
12
13 53 Meikle and Taylor-Walsh, 1984).
14
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16
17 54 Tinnitus represents a major financial burden to the healthcare system. For example, in
18
19 55 England there are approximately 0.75 million primary care consultations each year where the
20
21 56 primary complaint is tinnitus (El-Shunnar et al., 2011) and the average cost to the National
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23 57 Health System of tinnitus treatment per year is estimated to be GB£750M. The estimated
24
25 58 annual societal costs of tinnitus in the UK is GB£2.7 billion (Stockdale et al., 2017).
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29
30 59 There is currently no gold standard treatment for tinnitus, rather, various management
31
32 60 strategies are used or have been trialled. Those include education and information, sound-
33
34 61 based interventions, psychology-based interventions, self-help interventions, relaxation
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36 62 therapy, pharmacology-based interventions, manual physical therapy, magnetic stimulation,
37
38 63 electrical stimulation, complementary and alternative therapies, and combination of two or
39
40 64 more approaches (complex interventions). Guidelines for the management of tinnitus have
41
42 65 been developed in the USA and Europe (Cima et al., 2019; Fuller et al., 2017a). In the UK,
43
44 66 there are commissioning guidelines for tinnitus services for adults (Department of Health,
45
46 67 2009), and clinical practice guidance for the assessment and management of tinnitus in
47
48 68 children (British Society of Audiology, 2015) A Clinical Knowledge Summary has been
49
50 69 produced by the National Institute for Health and Care Excellence (NICE) and two national
51
52 70 guidelines are in development: the first by NICE; the second by the British Society of
53
54 71 Audiology (BSA). NICE has published the scope of the guidelines that are in development
55
56 72 (<https://www.nice.org.uk/guidance/gid-ng10077/documents/final-scope>) outlining which
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1 *Sereda et al. Prioritising topics for systematic review*

2
3 73 factors will and will not be considered by the guidelines. Effective guidelines can only be
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5 74 developed if there is strong evidence-based information available. If such high-level evidence
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7 75 is not available, recommendations arising from the guidelines are weak and clinically
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10 76 ineffective. These are just some of the drivers for prioritising new and updating existing
11
12 77 Cochrane systematic reviews of interventions for tinnitus.
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18 79 **METHODS**

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21 80 The prioritisation process was conducted in two stages. First, a scoping review was
22
23 81 conducted to estimate the volume of randomised controlled trial (RCT) level evidence
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25 82 available, to facilitate prioritisation, to aid in the design of a template protocol, and to
26
27 83 estimate the work involved in conducting a suite of priority reviews. Secondly, interventions
28
29 84 were prioritised for review according to a set of pre-defined criteria.
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33 85 **Scoping review**

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36 86 We followed the methodological framework of Arksey and O'Malley (2005). This consisted
37
38 87 of: (1) identifying potentially relevant records; (2) selecting relevant records; (3) extracting
39
40 88 data items; and (4) collating, summarising, and reporting the results. The PRISMA-ScR
41
42 89 checklist (Tricco et al., 2018) guided reporting of the methods and results of the scoping
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44 90 review.
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48 91 **Search strategy**

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51 92 In July 2017 we conducted a search of the Cochrane ENT Trials Register (via the Cochrane
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53 93 Register of studies) for RCTs. There were no language, publication year, or publication status
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55 94 restrictions. The search was run in the Cochrane ENT Register
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2
3 95 (<https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register>) using the
4
5 96 following strategy:

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7
8 97 1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND INREGISTER

9
10
11 98 2 tinnit* AND INREGISTER

12
13
14 99 3 #1 OR #2 AND INREGISTER,

15
16
17 100 where MESH DESCRIPTOR – Medical Subject Headings: The National Library of Medicine
18
19 101 controlled vocabulary thesaurus, INREGISTER – in the Cochrane ENT register, EXPLODE
20
21 102 ALL – search for selected subject heading (Tinnitus) and all of the subject headings in its
22
23 103 family.

24
25
26
27 104 The Cochrane ENT Register is populated using the methods described on the Cochrane ENT
28
29 105 website (<https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register>).

30
31 106 We also searched the Cochrane database of Systematic Reviews for all published reviews and
32
33 107 protocols for Cochrane reviews with ‘tinnitus’ in the title.

34
35 108 ***Selection of studies***

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38 109 Three authors (MS, DJH, DAH) independently screened all abstracts to determine eligibility
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40 110 for inclusion in the scoping review. Records were carried forward for full screening if at least
41
42 111 one of the authors selected it. We considered multiple articles reporting the same trial
43
44 112 together as a single record. Disagreements were discussed between authors until a consensus
45
46 113 was reached. Records were considered for inclusion according to PICOS (Methley et al.,
47
48 114 2014), as follows:

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52 115 ***Population:*** Children and/or adults with subjective tinnitus

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55 116 ***Intervention:*** All interventions for subjective tinnitus

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58 117 ***Comparator:*** No intervention (e.g. waiting list), different intervention, placebo

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2
3 118 **Outcome:** Did not form an inclusion criterion

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6 119 **Study design:** Randomised controlled trials only.

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9 120 ***Data extraction***

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12 121 Data were extracted using a bespoke template form designed by the authors (MS and DJH),
13
14 122 piloted on a subset of records, and revised before formal data extraction was undertaken.

15
16 123 PICOS data were extracted (population, intervention, comparator, outcomes, and outcome
17
18 124 measures used, and study design). Two authors independently extracted the data.

19
20
21
22 125 For each intervention, we recorded whether there were existing RCTs, the number of RCTs,

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24 126 and whether those RCTs were included or not in existing Cochrane reviews. In scoping the

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26 127 literature, drug trials were catalogued (by DMcF) according to the World Health

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28 128 Organization (WHO) Collaborating Centre for Drug Statistics Methodology Anatomical

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30
31 129 Therapeutic Chemical (ATC) Classification System (https://www.whocc.no/atc_ddd_index/).

32
33
34 130 ***Methodological assessment of published Cochrane reviews***

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37 131 A list of published Cochrane systematic reviews and published Cochrane protocols was

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39 132 populated. When judging whether an existing Cochrane systematic review required updating

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41 133 or replacing, we considered the date of the most recent literature search of the review, and

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43 134 whether ongoing studies were identified in those reviews. Both of these factors were used to

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45 135 consider whether there was new research that may alter the estimates of effect, the quality of

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47 136 the overall evidence, or the conclusions drawn in the published review. Other methodological

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49 137 aspects of the systematic reviews were assessed including (1) whether a Preferred Reporting

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51 138 Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was included; (2)

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53 139 whether the latest risk of bias tool was used; (3) whether a ‘Summary of Findings (SoF)’

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56 140 table was included; (4) whether the ‘Grading of Recommendations, Assessment,

1 *Sereda et al. Prioritising topics for systematic review*

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3 141 Development and Evaluation' (GRADE; <https://gradepro.org/>) tool was used (Schünemann et
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5 142 al., 2013); (5) whether the assessed outcomes included measures of benefits and harms of the
6
7 143 intervention; and (6) whether the review included all of the methods sections currently
8
9 144 recommended by Cochrane (Higgins and Green, 2011).

13 145 **Prioritisation process**

16 146 Authors of this scoping review were experts in tinnitus (clinical researchers, a psychologist,
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18 147 ENT surgeon, and an audiologist) or experts in Cochrane systematic review methodology. All
19
20 148 authors took part in agreeing the criteria that were used to prioritise reviews. Firstly a list of
21
22 149 criteria was populated including criteria formulated according to the remit from National
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24 150 Institute for Health Research (NIHR) with additional criteria proposed by individual authors.
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26 151 Secondly authors ranked these criteria in order of importance. Based on the ranking, four
27
28 152 primary and four secondary criteria were formulated.

30 153 Primary criteria were whether:

- 33 154 1. the intervention was available for tinnitus management within the National Health
34
35 155 Service (NHS) When considering drug treatments for tinnitus, this included drugs
36
37 156 that were used on-licence such as betahistine for Ménière's disease-associated
38
39 157 tinnitus. It also included drugs used that have been recorded as being used off-
40
41 158 licence as a primary tinnitus treatment (Langguth et al., 2009; Hall et al., 2011;
42
43 159 McFerran et al., 2018). It did not include drugs used primarily for treating comorbid
44
45 160 conditions.
- 46 161 2. the intervention was included in the NICE document, *Guidelines scope. Tinnitus:*
47
48 162 *assessment and management.* ([ng10077/documents/final-scope](https://www.nice.org.uk/guidance/gid-
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60)). This document outlined the proposed contents of the
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163 forthcoming NICE Guideline.

1 *Sereda et al. Prioritising topics for systematic review*

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- 3 165 3. there was ‘no recommendation’ or disagreement in recommendations for an
- 4
- 5 166 intervention within or between current management guidelines
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- 8 167 4. existing Cochrane systematic reviews concluded there was a lack of evidence for an
- 9
- 10 168 intervention, but additional evidence is now available or if there was no current
- 11
- 12 169 Cochrane review.
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15 170 Secondary criteria were whether:

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- 18 171 5. the intervention was already prioritised by healthcare users and healthcare
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- 20 172 practitioners in the James Lind Alliance Priority Setting Partnership for tinnitus as a
- 21
- 22 173 ‘top 10’ treatment uncertainty.
- 23
- 24
- 25 174 6. there were sufficient new RCTs for a new or updated review to be meaningful.
- 26
- 27 175 7. interventions were referred to in the tinnitus research network (TINNET) European
- 28
- 29 176 clinical practice guideline.
- 30
- 31 177 8. there was evidence for variability in clinical practice, within or across countries.
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35 178 All methodological considerations, and importance to key stakeholders were considered

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37 179 together in prioritising updated and new systematic reviews. For each of the interventions

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39 180 authors judged how many of the primary and secondary criteria were met. From this a list of

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41 181 high priority reviews was formulated.

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48 183 **RESULTS**

49 184 **Summary of existing Cochrane reviews**

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51 185 The Cochrane Library contained 10 existing Cochrane reviews on tinnitus: amplification with

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53 186 hearing aids (Hoare et al., 2014), anticonvulsant drugs (Hoekstra et al., 2011), antidepressant

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55 187 drugs (Baldo et al., 2012), Cognitive Behavioural Therapy (CBT) (Martinez-Devesa et al.,

56

57 188 2010), Ginkgo biloba (Hilton et al., 2013), hyperbaric oxygen (for idiopathic sudden

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1 *Sereda et al. Prioritising topics for systematic review*

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3 189 sensorineural hearing loss and tinnitus) (Bennett et al., 2012), repetitive Transcranial
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5 190 Magnetic Stimulation (rTMS) (Meng et al., 2011), sound therapy (masking) (Hobson et al.,
6
7
8 191 2012), Tinnitus Retraining Therapy (TRT) (Phillips and McFerran, 2010a), and zinc
9
10 192 supplements (Person et al., 2016). A further eight protocols for systematic reviews had been
11
12 193 published. Four were protocols for reviews in progress: CBT (Fuller et al., 2017b), glutamate
13
14 194 receptor antagonists (Imsuwansri et al., 2016), melatonin (Ajayi et al., 2014), and
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16
17 195 neuromodulation (desynchronisation) (Hoare et al., 2015). In the review of TRT (Phillips and
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19 196 McFerran, 2010a), the literature search unearthed a number of studies that purported to be
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21 197 TRT but on inspection did not adhere to the strict protocol described by the developers of
22
23
24 198 TRT (Jastreboff and Hazell, 2004). Many of these studies observed the underlying principles
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26 199 of TRT and its scientific rationale which is generally referred to as the neurophysiological
27
28 200 model of tinnitus (Jastreboff, 1990). The authors of the TRT Cochrane review therefore
29
30 201 proposed to write a separate review of these studies which they described as modified TRT.
31
32
33 202 After discussion it was decided that a single review of both standard (unmodified) TRT and
34
35 203 modified TRT would be more appropriate and a protocol for a review was published (Phillips
36
37
38 204 and McFerran, 2010b). However, progress on this new review was suspended at the
39
40 205 suggestion of Cochrane. Methods in this protocol were judged as needing updating.
41
42
43 206 The other three published protocols (acupuncture (Li et al., 2016), low-level laser therapy
44
45 207 (Peng et al., 2014), and an overview of systematic reviews of interventions (Maldonado
46
47 208 Fernández et al., 2015) were withdrawn before the reviews were conducted or completed.
48
49 209 Eight of the 10 published Cochrane reviews were assessed as having outdated methods by the
50
51 210 Cochrane methodologist (EA). The review of zinc supplementation was judged as up-to-date
52
53
54 211 and the methods robust (Person et al., 2016). The review of amplification with hearing aids
55
56 212 was judged to have up-to-date methods such that the decision to update would depend on
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1 *Sereda et al. Prioritising topics for systematic review*

2
3 213 whether additional RCTs were identified. The number of records included in each of the 10
4
5 214 Cochrane reviews was between one and eight.

8 215 **New trials for potential inclusion in Cochrane reviews**

9
10 216 Scoping searches identified 1080 records (Figure 1). Based on title/abstract screening 731
11
12 217 records were selected for full text screening by at least one author. A further 318 records
13
14 218 were excluded that were duplicates (n=127), out of scope (n=11), not randomised (n=86),
15
16
17 219 conference abstracts with no results published (n=70), or required translation for which we
18
19 220 did not have the resources (Chinese, Japanese, Swedish, Spanish; n=15). Nine abstracts/full
20
21 221 texts were not available. An additional 24 records were identified from lists of references of
22
23 222 systematic reviews bringing the total number of records for full text screening and data
24
25 223 charting to 437. Among those, 365 records were identified that were new (not covered in
26
27 224 existing Cochrane reviews) RCTs with published results: PICOS data were extracted from
28
29 225 those records. In addition, 51 unpublished registered randomised trials were identified and
30
31 226 data regarding PICOS and trial status were extracted.

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37 228 *** INSERT FIGURE 1 ABOUT HERE***

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39 229

40 230 ***Education and information***

41
42 231 Eight trials were identified that examined information or education.

43 232 ***Sound-based interventions***

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45 233 Forty-three new trials of sound-based interventions were identified. The interventions trialled
46
47 234 included: 1) Amplification only devices (n=8); 2) Sound generator only devices (sometimes
48
49 235 referred to as maskers; n=20); 3) Combination devices (i.e. combined amplification and
50
51 236 sound generators; n=5); 4) Acoustic Coordinated Reset (CR) Neuromodulation (n=3); 5)
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1 *Sereda et al. Prioritising topics for systematic review*

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3 237 Phase-tailored sound treatment (n=1); 6) Spectrally tailored sound treatment (n=2); and 7)

4
5 238 Auditory training (n=4).

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8 239 ***Psychology-based interventions***

9
10 240 Thirty-nine new trials of psychology-based intervention were identified. Thirty-three of those
11
12 241 trialled CBT interventions and three trialled counselling. For the purpose of this scoping
13
14 242 review we included all studies using cognitive and/or behavioural approaches to treatment. It
15
16 243 is worth noting that there is a published protocol for a revision of the Cochrane review of
17
18 244 CBT for tinnitus (Fuller et al., 2017a). This review will examine all interventions for tinnitus
19
20 245 that include cognitive, and/or behavioural interventions. Those would include Acceptance
21
22 246 and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different
23
24 247 ‘waves’ of CBT.

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28
29 248 ***Self-help interventions***

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31 249 One trial was identified that examined a self-help intervention, namely an online discussion
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33 250 forum.

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37 251 ***Relaxation therapy***

38
39 252 Eighteen trials of relaxation therapy were identified including: Neurofeedback/Biofeedback
40
41 253 (n=8); Hypnosis/Hypnotherapy (n=3); 3) Relaxation (n=7).

42
43
44 254 ***Pharmacology-based interventions***

45
46 255 One hundred and fifty-eight new trials of pharmacological interventions for tinnitus were
47
48 256 identified. They were classified in nine different categories based on the WHO ATC system:
49
50 257 1) Alimentary tract and metabolism (n=12); 2) Blood and blood forming organs (n=8); 3)
51
52 258 Cardiovascular system (n=20); 4) Genito-urinary system and sex hormones (n=5); 5)
53
54 259 Musculo-skeletal system (n=3); 6) Nervous system (n=83); 7) Respiratory system (n=1); 8)

1 *Sereda et al. Prioritising topics for systematic review*

2
3 260 Systemic hormonal preparations, excluding sex hormones and insulins (n=8); and 9) Various
4
5 261 (n=2). Thirteen trials of non-classified (i.e. experimental) medications were also identified.

7
8 262 ***Manual physical therapy***

9
10 263 Five trials of manual physical therapy were identified including: 1) Cervical spine treatment
11
12 264 (n=3); 2) Myofascial trigger point deactivation (n=1); and 3) Temporomandibular Joint
13
14 265 Treatment (n=1).

17
18 266 ***Magnetic stimulation***

19
20
21 267 Forty-one trials of magnetic stimulation were identified: 1) Repetitive Transcranial Magnetic
22
23 268 Stimulation (rTMS, n=36), 2) Continuous Theta Burst Stimulation (cTBS, n=2); 3) Deep
24
25 269 Transcranial Magnetic Stimulation (n=1); 4) Electromagnetic Ear Stimulation (n=1); and 5)
26
27 270 Rare-earth magnets placed close to the tympanic membrane (n=1).

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29
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31 271 ***Electrical stimulation***

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33
34 272 Twenty-three new trials of electrical stimulation were identified including: 1) Cochlear
35
36 273 implant (n=3); 2) Transcranial Alternating Current Stimulation (tACS; n=1); 3) Transcranial
37
38 274 Direct Current Stimulation (tDCS; n=11); 4) Vagus Nerve Stimulation (VNS; n=3); 5)
39
40 275 Transcutaneous Electrical Nerve Stimulation (TENS; n=2); 6) Ear electrical stimulation via
41
42 276 surface tympanic electrode (n=1); and 7) External electrical stimulation via mastoid bones
43
44 277 (n=1). According to the published Cochrane protocol of neuromodulation
45
46 278 (desynchronisation) for tinnitus (Hoare et al., 2015), all trials of electrical stimulation for
47
48 279 tinnitus are likely to be included.

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53 280 ***Complementary and alternative therapies***

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56 281 Fifty-six trials of complementary and alternative therapies were identified including: 1)
57
58 282 Acupuncture (n=26); 2) Dietary supplements and herbal remedies (n=10); 3) Laser treatment
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1 *Sereda et al. Prioritising topics for systematic review*

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3 283 (n=14); 4) Ozone (n=1); 5) Ultrasound (n=2); 6) Vibratory stimulation (n=2); and 7) Virtual
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5 284 reality (n=1).

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7
8 285 ***Complex interventions***

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11 286 Twenty-four trials of complex interventions were identified including: 1) Heidelberg Neuro-
12
13 287 Music Therapy (n=2); 2) Perceptual/cognitive training (n=4); 3) Progressive Tinnitus
14
15 288 Management (PTM, n=4); 4) Tinnitus Retraining Therapy (TRT, including modified TRT;
16
17 289 n=9); 5) Combination of psychological approaches with other management strategies (n=3);
18
19 290 6) bimodal treatment involving TRT with EMDR and TRT with CBT (n=1); and 7) a
20
21 291 combination of sound based, educational and integrated medicine therapies (n=1).

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25 292 **Priority reviews on tinnitus**

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29 293 Three high priority reviews were identified based on the pre-defined priority criteria. Those
30
31 294 were: 1) sound therapy using amplification devices and/or sound generators for tinnitus; 2)
32
33 295 betahistine; 3) CBT.

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35
36 296 Sound therapy met the first three primary priority criteria, the existing Cochrane reviews
37
38 297 concluded a lack of evidence of clinical effectiveness (Hoare et al., 2014a, Hobson et al.,
39
40 298 2012) and new trials were identified. Our recommendation was that a priority Cochrane
41
42 299 review should include amplification only devices, combination devices (combined
43
44 300 amplification and sound generation), and sound generators. Suggested comparisons for
45
46 301 inclusion were: 1) Amplification only vs waiting-list control, placebo, education/information
47
48 302 only with no device; 2) Combination devices vs waiting-list control, placebo,
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50 303 education/information only with no device, amplification only, sound generator only; 3)
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52 304 Sound generator only vs waiting-list control, placebo, education/information only with no
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54 305 device. Trials that have conditions that explicitly included counselling (such as TRT, PTM,
55
56 306 Neuromonics) should be excluded. Counselling was defined according to Culley and Bond

1 *Sereda et al. Prioritising topics for systematic review*

2
3 307 (2011) as a process that aims to empower patients to reach decisions and take actions for
4
5 308 themselves. Establishing a therapeutic relationship, clarifying and defining problems,
6
7 309 planning actions, and managing expectations are all key features of the approach. Education
8
9 310 and information giving can be entirely one-way, whereas counselling is about empowerment
10
11 311 and enabling patients to arrive at their own solutions using their own internal resources.
12
13 312 Therefore, unless there were explicit efforts and description of a process towards
14
15 313 empowerment in trial reports, and a trained therapist delivered it, then it was not considered
16
17 314 counselling. Betahistine also met the first three primary priority criteria and there is no
18
19 315 existing Cochrane review. We identified six trials for consideration. Comparisons should
20
21 316 include placebo, no intervention, education and information only. However, it should be
22
23 317 noted that only three trials include the above comparisons (n=3) and the others would not be
24
25 318 suitable for synthesis. Subgroup analyses with and without Ménière's disease should also be
26
27 319 considered, but we note that there is an existing Cochrane review on Betahistine for
28
29 320 Ménière's disease or syndrome which has impact on tinnitus symptom severity as a
30
31 321 secondary outcome (Van Esch et al., 2018).
32
33 322 CBT met the first three primary priority criteria. Although there is an existing Cochrane
34
35 323 review (Martinez-Devesa et al., 2010) it is now outdated and does not include all cognitive,
36
37 324 and/or behavioural interventions (Acceptance and Commitment Therapy (ACT) and
38
39 325 Mindfulness-based therapies, described as different 'waves' of CBT). A Cochrane review
40
41 326 examining all cognitive and behavioural approaches for tinnitus is currently ongoing (Fuller
42
43 327 et al., 2017b).
44
45 328 Further priorities (meeting fewer priority criteria) included: 1) Gingko biloba; 2) anxiolytics;
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47 329 3) hypnotics; 4) antiepileptics; 5) neuromodulation.
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1 *Sereda et al. Prioritising topics for systematic review*

2
3 330 Gingko biloba met the first two primary priority criteria. The existing Cochrane review
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5 331 concluded a lack of evidence for effectiveness (Hilton et al., 2013) and new trials were
6
7 332 identified. Suggested comparisons include placebo, no intervention, education and
8
9
10 333 information only. Anxiolytics met the first two primary criteria and there is no existing
11
12 334 Cochrane review. Nine trials have been identified which may be eligible. Suggested
13
14 335 comparisons are placebo, no intervention, education and information only. Hypnotics meets
15
16 336 the first two primary criteria and there is no existing Cochrane review. Eight trials have been
17
18 337 identified which may be eligible for inclusion. Suggested comparisons are placebo, no
19
20 338 intervention, education and information only. Antiepileptics met the first two primary criteria
21
22 339 and there is no existing Cochrane review. Eleven trials have been identified. Suggested
23
24 340 comparisons include placebo, no intervention, education and information only.
25
26 341 Neuromodulation met two primary criteria including being in scope of the NICE guidelines.
27
28 342 However, a Cochrane review of neuromodulation for tinnitus is currently ongoing (Hoare et
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30 343 al., 2015).
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42 346 **CONCLUSIONS**

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45 347 This technical report highlights a comprehensive exercise we undertook to prioritise topics of
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47 348 unmet need for high-quality systematic review in tinnitus management.
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50 349 Importantly, these priority reviews will respond to unanswered questions identified in current
51
52 350 and developing clinical practice guidelines for tinnitus. Three high priority reviews are
53
54 351 recommended: 1) sound therapy using amplification devices and/or sound generators for
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56 352 tinnitus; 2) betahistine; 3) Cognitive Behaviour Therapy. Further priorities are: 4) Gingko
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58 353 biloba; 5) anxiolytics; 6) hypnotics; 7) antiepileptics; 8) neuromodulation.
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1 *Sereda et al. Prioritising topics for systematic review*

2
3 354 Applying a prioritisation process ensures that resources are invested most effectively in work
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5 355 that meets the needs of funders and stakeholders and addresses known discrepancies or gaps
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7 356 in clinical knowledge. This particular prioritisation work focused on UK clinical practice for
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9 357 tinnitus and therefore the relevant priority criteria, such as availability of the intervention
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11 358 within the NHS and inclusion in the scope of the NICE tinnitus guideline. However, the
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13 359 process can easily be adapted to a range of international, national or local settings and
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15 360 priorities. For example, regional or country-specific clinical practice can be taken into
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17 361 consideration as well as guidelines at the national, regional or international level (e.g.
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19 362 European or country-specific) when formulating the priority criteria.
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24 363 The scoping exercise described here has already resulted in the expedited production of two
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26 364 Cochrane systematic reviews (Sereda et al., 2018; Wegner et al., 2018) in part to inform the
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28 365 NICE guideline on tinnitus which is currently under development. A further three priority
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30 366 reviews are currently in progress (Fuller et al., 2017b; Hoare et al. 2015; and Gingko biloba –
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32 367 protocol in preparation).
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1 *Sereda et al. Prioritising topics for systematic review*

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40 531 **FIGURE LEGEND**

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43 532 Figure 1. Flow diagram illustrating search strategy and scoping review stages

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48 534 **SUPPLEMENTAL MATERIAL**

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50 535 Supplemental material 1. Summary of priority criteria for each of the interventions

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Sereda et al. Prioritising topics for systematic review

1 ABSTRACT

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

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

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

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

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

20
21
22 **Keywords:** Cochrane, systematic review, priority, management, treatment, tinnitus
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1 *Sereda et al. Prioritising topics for systematic review*

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INTRODUCTION

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9 26 Systematic reviews and meta-analyses represent the highest level of evidence for the
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11 27 effectiveness of clinical interventions and hold a critical place in informing health policy and
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14 28 evidence-based practice ([Greenwell et al.2016; Morata et al., 2017](#)). One of the foremost
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16 29 organisations producing systematic reviews is Cochrane, which is a UK based charity (not-
17
18 30 for-profit organisation) that supervises a global independent network of healthcare
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20 31 practitioners, researchers, patient advocates and others. It represents more than 11,000
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22 32 members and over 68,000 supporters from over 130 countries
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24 33 (<https://www.cochrane.org/about-us>). Cochrane authors conduct systematic reviews of
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26 34 health-care interventions and diagnostic tests which are published as Cochrane Reviews in
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28 35 the Cochrane Library. Previously, Cochrane authors self-selected topics for their reviews and
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30 36 submitted proposals to Cochrane for approval. This process has been updated and now,
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32 37 Cochrane groups are encouraged to work strategically to respond to the needs of funders and
33
34 38 key stakeholders to produce reviews on topics of the highest priority to users. One approach
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36 39 to prioritising these reviews is to conduct a scoping exercise (<https://ent.cochrane.org/our->
37
38 40 [evidence/prioritisation/scoping-projects](https://ent.cochrane.org/our-evidence/prioritisation/scoping-projects)). Cochrane Ear, Nose, & Throat Disorders (Cochrane
39
40 41 ENT) group this has developed suites of reviews with an “optimal, shared protocol with a
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42 42 well-designed and consistent set of outcome measures” (Cochrane ENT Group, 2019).
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44 43 In this report we describe a comprehensive exercise used to prioritise systematic reviews of
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46 44 interventions for tinnitus conducted for the Cochrane ENT group.
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51 45 Subjective tinnitus is described as the perception of sound in the absence of an external sound
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53 46 source (Jastreboff and Hazell, 2004). It is a symptom experienced by 10-30% of the adult
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55 47 population (McCormack et al., 2016). About 20% of people with tinnitus experience it as
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Sereda et al. Prioritising topics for systematic review

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

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

59 There is currently no gold standard treatment for tinnitus, rather, various management
60 strategies are used or have been trialled. Those include education and information, sound-
61 based interventions, psychology-based interventions, self-help interventions, relaxation
62 therapy, pharmacology-based interventions, manual physical therapy, magnetic stimulation,
63 electrical stimulation, complementary and alternative therapies, and combination of two or
64 more approaches (complex interventions). Guidelines for the management of tinnitus have
65 been developed in the USA and Europe (Cima et al., 2019; Fuller et al., 2017a). In the UK,
66 there are commissioning guidelines for tinnitus services for adults (Department of Health,
67 2009), and clinical practice guidance for the assessment and management of tinnitus in
68 children (British Society of Audiology, 2015) A Clinical Knowledge Summary has been
69 produced by the National Institute for Health and Care Excellence (NICE) and two national
70 guidelines are in development: the first by NICE; the second by the British Society of
71 Audiology (BSA). NICE has published the scope of the guidelines that are in development
72 (<https://www.nice.org.uk/guidance/gid-ng10077/documents/final-scope>) outlining which

1 *Sereda et al. Prioritising topics for systematic review*

2
3 73 factors will and will not be considered by the guidelines. Effective guidelines can only be
4
5 74 developed if there is strong evidence-based information available. If such high-level evidence
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7 75 is not available, recommendations arising from the guidelines are weak and clinically
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9
10 76 ineffective. These are just some of the drivers for prioritising new and updating existing
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12 77 Cochrane systematic reviews of interventions for tinnitus.
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18 79 **METHODS**

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21 80 The prioritisation process was conducted in two stages. First, a scoping review was
22
23 81 conducted to estimate the volume of randomised controlled trial (RCT) level evidence
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25 82 available, to facilitate prioritisation, to aid in the design of a template protocol, and to
26
27 83 estimate the work involved in conducting a suite of priority reviews. Secondly, interventions
28
29 84 were prioritised for review according to a set of pre-defined criteria.
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31

33 85 **Scoping review**

34
35
36 86 We followed the methodological framework of Arksey and O'Malley (2005). This consisted
37
38 87 of: (1) identifying potentially relevant records; (2) selecting relevant records; (3) extracting
39
40 88 data items; and (4) collating, summarising, and reporting the results. The PRISMA-ScR
41
42 89 checklist (Tricco et al., 2018) guided reporting of the methods and results of the scoping
43
44 90 review.
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46

48 91 **Search strategy**

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51 92 In July 2017 we conducted a search of the Cochrane ENT Trials Register (via the Cochrane
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53 93 Register of studies) for RCTs. There were no language, publication year, or publication status
54
55 94 restrictions. The search was run in the Cochrane ENT Register
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1 *Sereda et al. Prioritising topics for systematic review*

2
3 95 (<https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register>) using the
4
5 96 following strategy:

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7
8 97 1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND INREGISTER

9
10
11 98 2 tinnit* AND INREGISTER

12
13
14 99 3 #1 OR #2 AND INREGISTER,

15
16
17 100 where MESH DESCRIPTOR – Medical Subject Headings: The National Library of Medicine
18
19 101 controlled vocabulary thesaurus, INREGISTER – in the Cochrane ENT register, EXPLODE
20
21 102 ALL – search for selected subject heading (Tinnitus) and all of the subject headings in its
22
23 103 family.

24
25
26
27 104 The Cochrane ENT Register is populated using the methods described on the Cochrane ENT
28
29 105 website (<https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register>).

30
31 106 We also searched the Cochrane database of Systematic Reviews for all published reviews and
32
33 107 protocols for Cochrane reviews with ‘tinnitus’ in the title.

34
35 108 ***Selection of studies***

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37
38 109 Three authors (MS, DJH, DAH) independently screened all abstracts to determine eligibility
39
40 110 for inclusion in the scoping review. Records were carried forward for full screening if at least
41
42 111 one of the authors selected it. We considered multiple articles reporting the same trial
43
44 112 together as a single record. Disagreements were discussed between authors until a consensus
45
46 113 was reached. Records were considered for inclusion according to PICOS (Methley et al.,
47
48 114 2014), as follows:

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50
51 115 ***Population:*** Children and/or adults with subjective tinnitus

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53 116 ***Intervention:*** All interventions for subjective tinnitus

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56 117 ***Comparator:*** No intervention (e.g. waiting list), different intervention, placebo

1 *Sereda et al. Prioritising topics for systematic review*

2
3 118 **Outcome:** Did not form an inclusion criterion

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6 119 **Study design:** Randomised controlled trials only.

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9 120 ***Data extraction***

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11
12 121 Data were extracted using a bespoke template form designed by the authors (MS and DJH),
13
14 122 piloted on a subset of records, and revised before formal data extraction was undertaken.

15
16 123 PICOS data were extracted (population, intervention, comparator, outcomes, and outcome
17
18 124 measures used, and study design). Two authors independently extracted the data.

19
20
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22 125 For each intervention, we recorded whether there were existing RCTs, the number of RCTs,

23
24 126 and whether those RCTs were included or not in existing Cochrane reviews. In scoping the

25
26 127 literature, drug trials were catalogued (by DMcF) according to the World Health

27
28 128 Organization (WHO) Collaborating Centre for Drug Statistics Methodology Anatomical

29
30 129 Therapeutic Chemical (ATC) Classification System (https://www.whocc.no/atc_ddd_index/).

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34 130 ***Methodological assessment of published Cochrane reviews***

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37 131 A list of published Cochrane systematic reviews and published Cochrane protocols was

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39 132 populated. When judging whether an existing Cochrane systematic review required updating

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41 133 or replacing, we considered the date of the most recent literature search of the review, and

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43 134 whether ongoing studies were identified in those reviews. Both of these factors were used to

44
45 135 consider whether there was new research that may alter the estimates of effect, the quality of

46
47 136 the overall evidence, or the conclusions drawn in the published review. Other methodological

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49 137 aspects of the systematic reviews were assessed including (1) whether a Preferred Reporting

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51 138 Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram was included; (2)

52
53 139 whether the latest risk of bias tool was used; (3) whether a 'Summary of Findings (SoF)'

54
55
56 140 table was included; (4) whether the 'Grading of Recommendations, Assessment,

Sereda et al. Prioritising topics for systematic review

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

145 **Prioritisation process**

146 Authors of this scoping review were experts in tinnitus (clinical researchers, a psychologist,
147 ENT surgeon, and an audiologist) or experts in Cochrane systematic review

148 methodology. ~~Authors of this scoping review were experts in tinnitus, clinical researchers, a
149 psychologist, ENT surgeon, and an audiologist or experts in Cochrane systematic review~~

150 ~~methodology.~~ All authors took part in agreeing the criteria that were used to prioritise
151 reviews. Firstly a list of criteria was populated including criteria formulated according to the
152 remit from National Institute for Health Research (NIHR) with additional criteria proposed
153 by individual authors. Secondly authors ranked these criteria in order of importance. Based
154 on the ranking, four primary and four secondary criteria were formulated.

155 Primary criteria were whether:

156 1. the intervention is-was available for tinnitus management within the National Health
157 Service (NHS) When considering drug treatments for tinnitus, this included drugs
158 that are-were used on-licence such as betahistine for Ménière's disease-associated
159 tinnitus. It also included drugs used that have been recorded as being used off-
160 licence as a primary tinnitus treatment (Langguth et al., 2009; Hall et al., 2011;
161 McFerran et al., 2018). It did not include drugs used primarily for treating comorbid
162 conditions.

163 2. the intervention is-was included in the NICE document, *Guidelines scope. Tinnitus:
164 assessment and management.* (<https://www.nice.org.uk/guidance/gid->

1 *Sereda et al. Prioritising topics for systematic review*

2
3 165 [ng10077/documents/final-scope](#)). This document ~~outlines~~ outlined the proposed
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6 166 contents of the forthcoming NICE Guideline.

7
8 167 3. there was ‘no recommendation’ or disagreement in recommendations for an
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10 168 intervention within or between current management guidelines

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12 169 4. existing Cochrane systematic reviews concluded there was a lack of evidence for an
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14
15 170 intervention, but additional evidence is now available or if there ~~was~~ is no current
16
17 171 Cochrane review.

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20 172 Secondary criteria were whether:

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23 173 5. the intervention ~~had was~~ already ~~been~~ prioritised by healthcare users and healthcare
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25 174 practitioners in the James Lind Alliance Priority Setting Partnership for tinnitus as a
26
27 175 ‘top 10’ treatment uncertainty.

28
29
30 176 6. there were sufficient new RCTs for a new or updated review to be meaningful.

31
32 177 7. interventions were referred to in the tinnitus research network (TINNET) European
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34 178 clinical practice guideline.

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37 179 8. there was evidence for variability in clinical practice, within or across countries.

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40 180 All methodological considerations, and importance to key stakeholders were considered
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42 181 together in prioritising updated and new systematic reviews. For each of the interventions
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44 182 authors judged how many of the primary and secondary criteria were met. From this a list of
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46 183 high priority reviews was formulated.

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50 51 52 185 **RESULTS**

53 54 186 **Summary of existing Cochrane reviews**

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57 187 The Cochrane Library contained 10 existing Cochrane reviews on tinnitus: amplification with
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59 188 hearing aids (Hoare et al., 2014), anticonvulsant drugs (Hoekstra et al., 2011), antidepressant

Sereda et al. *Prioritising topics for systematic review*

189 drugs (Baldo et al., 2012), Cognitive Behavioural Therapy (CBT) (Martinez-Devesa et al.,
190 2010), Ginkgo biloba (Hilton et al., 2013), hyperbaric oxygen (for idiopathic sudden
191 sensorineural hearing loss and tinnitus) (Bennett et al., 2012), repetitive Transcranial
192 Magnetic Stimulation (rTMS) (Meng et al., 2011), sound therapy (masking) (Hobson et al.,
193 2012), Tinnitus Retraining Therapy (TRT) (Phillips and McFerran, 2010a), and zinc
194 supplements (Person et al., 2016). A further eight protocols for systematic reviews had been
195 published. Four were protocols for reviews in progress: CBT (Fuller et al., 2017b), glutamate
196 receptor antagonists (Imsuwansri et al., 2016), melatonin (Ajayi et al., 2014), and
197 neuromodulation (desynchronisation) (Hoare et al., 2015). In the review of TRT (Phillips and
198 McFerran, 2010a), the literature search unearthed a number of studies that purported to be
199 TRT but on inspection did not adhere to the strict protocol described by the developers of
200 TRT (Jastreboff and Hazell, 2004). Many of these studies observed the underlying principles
201 of TRT and its scientific rationale which is generally referred to as the neurophysiological
202 model of tinnitus (Jastreboff, 1990). The authors of the TRT Cochrane review therefore
203 proposed to write a separate review of these studies which they described as modified TRT.
204 After discussion it was decided that a single review of both standard (unmodified) TRT and
205 modified TRT would be more appropriate and a protocol for a review was published (Phillips
206 and McFerran, 2010b). However, progress on this new review was suspended at the
207 suggestion of Cochrane. Methods in this protocol were judged as needing updating. The other
208 three published protocols (acupuncture (Li et al., 2016), low-level laser therapy (Peng et al.,
209 2014), and an overview of systematic reviews of interventions (Maldonado Fernández et al.,
210 2015)) were withdrawn before the reviews were conducted or completed. There were 10
211 existing Cochrane reviews on tinnitus (Baldo et al., 2012; Bennett et al., 2012; Hilton et al.,
212 2013; Hoare et al., 2014; Hobson et al., 2012; Hoekstra et al., 2011; Martinez-Devesa et al.,
213 2010; Meng et al., 2011; Person et al., 2016; Phillips and McFerran, 2010a) published in The

1 *Sereda et al. Prioritising topics for systematic review*

2
3 214 ~~Cochrane Library. The interventions evaluated were Tinnitus Retraining Therapy (TRT),~~
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5 215 ~~Cognitive Behavioural Therapy (CBT), anticonvulsants, repetitive Transcranial Magnetic~~
6
7 216 ~~Stimulation (rTMS), antidepressants, sound therapy (masking), Ginkgo biloba, hyperbaric~~
8
9 217 ~~oxygen (for idiopathic sudden sensorineural hearing loss and tinnitus), zinc supplements, and~~
10
11 218 ~~amplification with hearing aids. A further eight protocols for systematic reviews had been~~
12
13 219 ~~published. Five were protocols for reviews in progress, on neuromodulation~~
14
15 220 ~~(desynchronisation) (Hoare et al., 2015), neurophysiological model-based treatments (Phillips~~
16
17 221 ~~and McFerran, 2010b), CBT (Fuller et al., 2017b), glutamate receptor antagonists~~
18
19 222 ~~(Imsuwansri et al., 2016), and melatonin (Ajayi et al., 2014). The other three published~~
20
21 223 ~~protocols (acupuncture, low-level laser therapy, and an overview of systematic reviews of~~
22
23 224 ~~interventions) were withdrawn before the reviews were conducted or completed (Li et al.,~~
24
25 225 ~~2016; Maldonado Fernández et al., 2015; Peng et al., 2014). The protocol for~~
26
27 226 ~~neurophysiological-based treatments for tinnitus (Phillips and McFerran, 2010b) planned to~~
28
29 227 ~~include unmodified and modified TRT, meaning it would constitute an update to the TRT~~
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31 228 ~~review. However, progress on this new review has been suspended at the suggestion of~~
32
33 229 ~~Cochrane. Methods in this protocol were judged as needing updating.~~

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40 230 Eight of the 10 published Cochrane reviews were assessed as having outdated methods by the
41
42 231 Cochrane methodologist (EA). The review of zinc supplementation was judged as up-to-date
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44 232 and the methods robust (Person et al., 2016). The review of amplification with hearing aids
45
46 233 was judged to have up-to-date methods such that the decision to update would depend on
47
48 234 whether additional RCTs were identified. The number of records included in each of the 10
49
50 235 Cochrane reviews was between one and eight.

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56 237 **New trials for potential inclusion in Cochrane reviews**

Sereda et al. *Prioritising topics for systematic review*

238 Scoping searches identified 1080 records (Figure 1). Based on title/abstract screening 731
239 records were selected for full text screening by at least one author. A further 318 records
240 were excluded that were duplicates (n=127), out of scope (n=11), not randomised (n=86),
241 conference abstracts with no results published (n=70), or required translation for which we
242 did not have the resources (Chinese, Japanese, Swedish, Spanish; n=15). Nine abstracts/full
243 texts were not available. An additional 24 records were identified from lists of references of
244 systematic reviews bringing the total number of records for full text screening and data
245 charting to 437. Among those, 365 records were identified that were new (not covered in
246 existing Cochrane reviews) RCTs with published results: PICOS data were extracted from
247 those records. In addition, 51 unpublished registered randomised trials were identified and
248 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

1 *Sereda et al. Prioritising topics for systematic review*

2
3 262 Thirty-nine new trials of psychology-based intervention were identified. Thirty-three of those
4
5 263 trialled CBT interventions and three trialled counselling. For the purpose of this scoping
6
7 264 review we included all studies using cognitive and/or behavioural approaches to treatment. It
8
9
10 265 is worth noting that there is a published protocol for a revision of the Cochrane review of
11
12 266 CBT for tinnitus (Fuller et al., 2017a). This review will examine all interventions for tinnitus
13
14 267 that include cognitive, and/or behavioural interventions. Those would include Acceptance
15
16 268 and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different
17
18
19 269 'waves' of CBT.

22 270 ***Self-help interventions***

25 271 One trial was identified that examined a self-help intervention, namely an online discussion
26
27 272 forum.

30 273 ***Relaxation therapy***

33 274 Eighteen trials of relaxation therapy were identified including: Neurofeedback/Biofeedback
34
35 275 (n=8); Hypnosis/Hypnotherapy (n=3); 3) Relaxation (n=7).

38 276 ***Pharmacology-based interventions***

41 277 One hundred and fifty-eight new trials of pharmacological interventions for tinnitus were
42
43 278 identified. They were classified in nine different categories based on the WHO ATC system:
44
45 279 1) Alimentary tract and metabolism (n=12); 2) Blood and blood forming organs (n=8); 3)
46
47 280 Cardiovascular system (n=20); 4) Genito-urinary system and sex hormones (n=5); 5)
48
49 281 Musculo-skeletal system (n=3); 6) Nervous system (n=83); 7) Respiratory system (n=1); 8)
50
51 282 Systemic hormonal preparations, excluding sex hormones and insulins (n=8); and 9) Various
52
53 283 (n=2). Thirteen trials of non-classified (i.e. experimental) medications were also identified.
54
55

57 284 ***Manual physical therapy***

1 *Sereda et al. Prioritising topics for systematic review*

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3 285 Five trials of manual physical therapy were identified including: 1) Cervical spine treatment
4
5 286 (n=3); 2) Myofascial trigger point deactivation (n=1); and 3) Temporomandibular Joint
6
7
8 287 Treatment (n=1).

9
10 288 ***Magnetic stimulation***

11
12
13 289 Forty-one trials of magnetic stimulation were identified: 1) Repetitive Transcranial Magnetic
14
15 290 Stimulation (rTMS, n=36), 2) Continuous Theta Burst Stimulation (cTBS, n=2); 3) Deep
16
17 291 Transcranial Magnetic Stimulation (n=1); 4) Electromagnetic Ear Stimulation (n=1); and 5)
18
19 292 Rare-earth magnets placed close to the tympanic membrane (n=1).
20
21
22

23 293 ***Electrical stimulation***

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25
26 294 Twenty-three new trials of electrical stimulation were identified including: 1) Cochlear
27
28 295 implant (n=3); 2) Transcranial Alternating Current Stimulation (tACS; n=1); 3) Transcranial
29
30 296 Direct Current Stimulation (tDCS; n=11); 4) Vagus Nerve Stimulation (VNS; n=3); 5)
31
32 297 Transcutaneous Electrical Nerve Stimulation (TENS; n=2); 6) Ear electrical stimulation via
33
34 298 surface tympanic electrode (n=1); and 7) External electrical stimulation via mastoid bones
35
36 299 (n=1). According to the published Cochrane protocol of neuromodulation
37
38 300 (desynchronisation) for tinnitus (Hoare et al., 2015), all trials of electrical stimulation for
39
40 301 tinnitus are likely to be included.
41
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43
44

45 302 ***Complementary and alternative therapies***

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48 303 Fifty-six trials of complementary and alternative therapies were identified including: 1)
49
50 304 Acupuncture (n=26); 2) Dietary supplements and herbal remedies (n=10); 3) Laser treatment
51
52 305 (n=14); 4) Ozone (n=1); 5) Ultrasound (n=2); 6) Vibratory stimulation (n=2); and 7) Virtual
53
54 306 reality (n=1).
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58 307 ***Complex interventions***

1 *Sereda et al. Prioritising topics for systematic review*

2
3 308 Twenty-four trials of complex interventions were identified including: 1) Heidelberg Neuro-
4
5 309 Music Therapy (n=2); 2) Perceptual/cognitive training (n=4); 3) Progressive Tinnitus
6
7 310 Management (PTM, n=4); 4) Tinnitus Retraining Therapy (TRT, including modified TRT;
8
9 n=9); 5) Combination of psychological approaches with other management strategies (n=3);
10
11 311
12 312 6) bimodal treatment involving TRT with EMDR and TRT with CBT (n=1); and 7) a
13
14 313 combination of sound based, educational and integrated medicine therapies (n=1).
15
16

17 314 **Priority reviews on tinnitus**

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20 315 Three high priority reviews were identified based on the pre-defined priority criteria. Those
21
22 316 were: 1) sound therapy using amplification devices and/or sound generators for tinnitus; 2)
23
24 317 betahistine; 3) CBT.
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27

28 318 Sound therapy met the first three primary priority criteria, the existing Cochrane reviews
29
30 319 concluded a lack of evidence of clinical effectiveness (Hoare et al., 2014a, Hobson et al.,
31
32 320 2012) and new trials were identified. Our recommendation was that a priority Cochrane
33
34 321 review should include amplification only devices, combination devices (combined
35
36 322 amplification and sound generation), and sound generators. Suggested comparisons for
37
38 323 inclusion were: 1) Amplification only vs waiting-list control, placebo, education/information
39
40 324 only with no device; 2) Combination devices vs waiting-list control, placebo,
41
42 325 education/information only with no device, amplification only, sound generator only; 3)
43
44 326 Sound generator only vs waiting-list control, placebo, education/information only with no
45
46 327 device. Trials that have conditions that explicitly included counselling (such as TRT, PTM,
47
48 328 Neuromonics) should be excluded. Counselling was defined according to Culley and Bond
49
50
51 329 (2011) as a process that aims to empower patients to reach decisions and take actions for
52
53 330 themselves. Establishing a therapeutic relationship, clarifying and defining problems,
54
55
56 331 planning actions, and managing expectations are all key features of the approach. Education
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Sereda et al. *Prioritising topics for systematic review*

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

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

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

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

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

1 *Sereda et al. Prioritising topics for systematic review*

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3 356 information only. Anxiolytics met the first two primary criteria and there is no existing
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5 357 Cochrane review. Nine trials have been identified which may be eligible. Suggested
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8 358 comparisons are placebo, no intervention, education and information only. Hypnotics meets
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10 359 the first two primary criteria and there is no existing Cochrane review. Eight trials have been
11
12 360 identified which may be eligible for inclusion. Suggested comparisons are placebo, no
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14 361 intervention, education and information only. Antiepileptics met the first two primary criteria
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16 362 and there is no existing Cochrane review. Eleven trials have been identified. Suggested
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18 363 comparisons include placebo, no intervention, education and information only.
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20
21 364 Neuromodulation met two primary criteria including being in scope of the NICE guidelines.
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23
24 365 However, a Cochrane review of neuromodulation for tinnitus is currently ongoing (Hoare et
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26 366 al., 2015).

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33 34 35 369 **CONCLUSIONS**

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38 370 This technical report highlights a comprehensive exercise we undertook to prioritise topics of
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40 371 unmet need for high-quality systematic review in tinnitus management.

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43 372 Importantly, these priority reviews will respond to unanswered questions identified in current
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45 373 and developing clinical practice guidelines for tinnitus. Three high priority reviews are
46
47 374 recommended: 1) sound therapy using amplification devices and/or sound generators for
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49 375 tinnitus; 2) betahistine; 3) Cognitive Behaviour Therapy. Further priorities are: 4) Gingko
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51 376 biloba; 5) anxiolytics; 6) hypnotics; 7) antiepileptics; 8) neuromodulation.

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55 377 Applying a prioritisation process ensures that resources are invested most effectively in work
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57 378 that meets the needs of funders and stakeholders and addresses known discrepancies or gaps
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59 379 in clinical knowledge. This particular prioritisation work focused on UK clinical practice for

1 *Sereda et al. Prioritising topics for systematic review*

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3 380 tinnitus and therefore the relevant priority criteria, such as availability of the intervention
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5 381 within the NHS and inclusion in the scope of the NICE tinnitus guideline. However, the
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7 382 process can easily be adapted to a range of international, national or local settings and
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9 383 priorities. For example, regional or country-specific clinical practice can be taken into
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11 384 consideration as well as guidelines at the national, regional or international level (e.g.
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13 385 European or country-specific) when formulating the priority criteria.
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17 386 The scoping exercise described here has already resulted in the expedited production of two
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19 387 Cochrane systematic reviews (Sereda et al., 2018; Wegner et al., 2018) in part to inform the
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21 388 NICE guideline on tinnitus which is currently under development. A further three priority
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23 389 reviews are currently in progress (Fuller et al., 2017b; Hoare et al. 2015; and Gingko biloba –
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25 390 protocol in preparation).
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30 554 **FIGURE LEGEND**

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33 555 Figure 1. Flow diagram illustrating search strategy and scoping review stages

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38 557 **SUPPLEMENTAL MATERIAL**

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40 558 Supplemental material 1. Summary of priority criteria for each of the interventions

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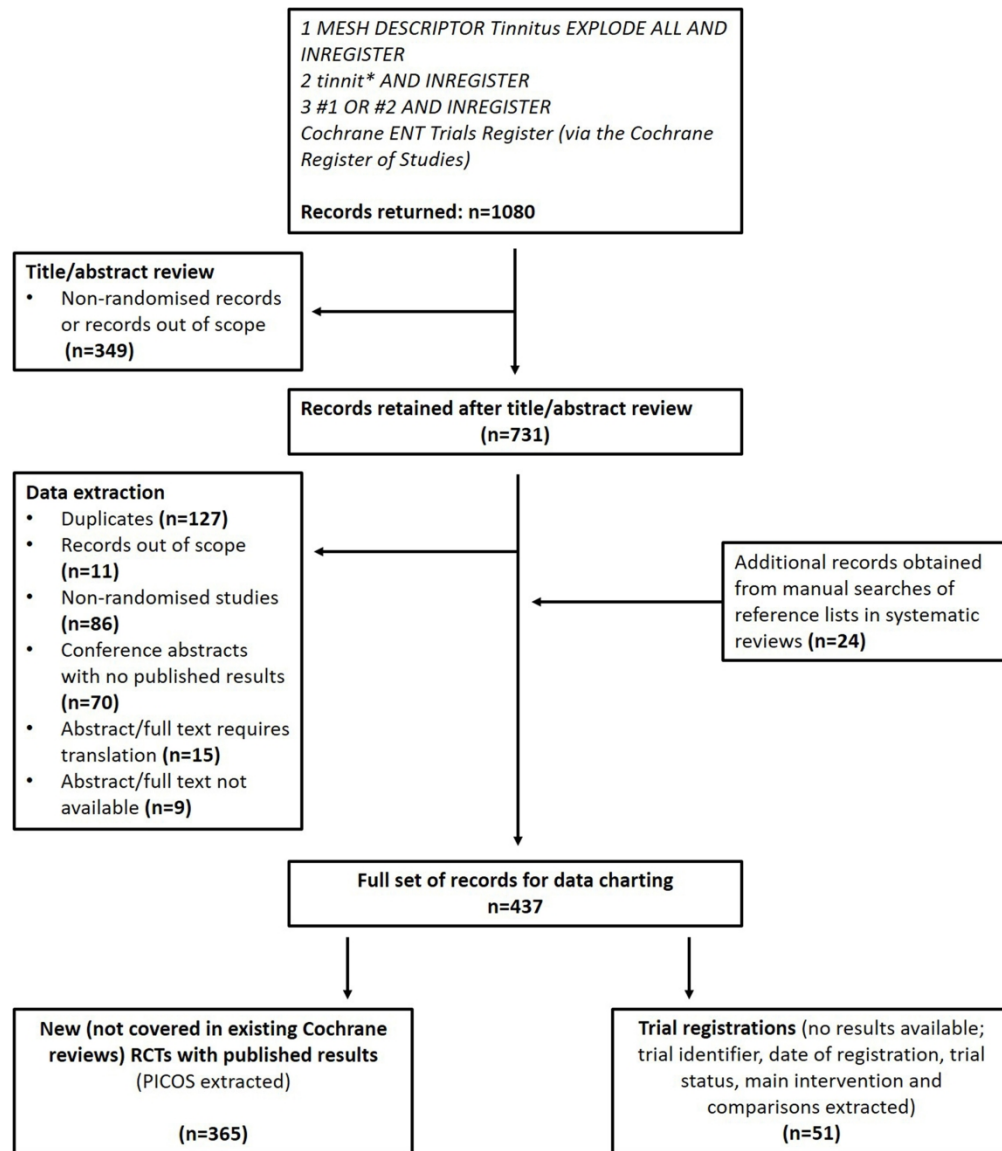


Figure 1. Flow diagram illustrating search strategy and scoping review stages

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.

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

1	<i>Antithrombotic agents</i>	YES	NO	YES	YES	YES	5	NO	YES
2	<i>Antianemic preparations</i>	NO	NO	YES	YES	YES	2	YES Vitamin B12	YES
3	Pharmacological approaches - Cardiovascular system								
4	<i>Antiarrhythmics</i>	YES	NO	YES	YES	YES	11	NO	YES
5	<i>Peripheral vasodilators</i>	YES	NO	YES	YES	YES	5	NO	YES
6	<i>Lipid modifying agents</i>	NO	NO	YES	YES	YES	1	NO	YES
7	<i>Other cardiac preparations</i>	YES	NO	YES	YES	YES	3	NO	YES
8	Pharmacological approaches - Genito-urinary system and sex hormones								
9	<i>Uterotonics</i>	NO	NO	YES	YES	YES	3	NO	YES
10	<i>Urologicals</i>	NO	NO	YES	YES	YES	2	NO	YES
11	Pharmacological approaches - Musculo-skeletal system								
12	<i>Anti-inflammatory and antirheumatic products</i>	YES	NO	YES	YES	YES	1	NO	YES
13	<i>Muscle relaxants</i>	NO	NO	YES	YES	YES	1	NO	YES
14	Pharmacological approaches – Nervous system								
15	<i>Anesthetics - General anesthetics</i>	NO	NO	YES	YES	YES	4	NO	YES
16	<i>Anesthetics - Local anesthetics</i>	YES	NO	YES	YES	YES	18	NO	YES
17	<i>Antiepileptics</i>	YES	NO	YES	YES	YES	11	YES Benzo- diazepines	YES
18	<i>Anti-Parkinson drugs</i>	YES	NO	YES	YES	YES	2	NO	YES

1	<i>Psycholeptics - Antipsychotics</i>	YES	NO	YES	YES	YES	2	NO	YES
2	<i>Psycholeptics - Anxiolytics</i>	YES	NO	YES	YES	YES	8	NO	YES
3									
4	<i>Hypnotics and sedatives</i>	YES	NO	YES	YES Melatonin	YES	8	YES Melatonin	YES
5									
6									
7	<i>Psychoanaleptics - Antidepressants</i>	YES	NO	YES	YES	YES	4	YES	YES
8									
9	<i>Psychostimulants and nootropics</i>	YES	NO	YES	YES	YES	1	NO	YES
10									
11	<i>Anti-dementia drugs</i>	YES	NO Ginkgo biloba	YES	YES	YES	6	YES	YES
12									
13									
14									
15	<i>Other nervous system drugs – Drugs used in addictive disorders</i>	NO	NO	YES	YES	YES	3	NO	YES
16									
17									
18	<i>Antivertigo preparations</i>	YES	YES Betahistine	YES	YES	YES	11	NO	YES
19									
20									
21									
22	<i>Combinations of medications</i>	NO	NO	YES	YES	YES	1	NO	YES
23									
24	Pharmacological approaches – respiratory system								
25									
26	<i>Respiratory stimulants</i>	YES	NO	YES	YES	YES	1	NO	YES
27									
28	Pharmacological approaches - Systemic hormonal preparations, excluding sex hormones and insulins								
29									
30	<i>Pituitary and hypothalamic hormones and analogues</i>	NO	NO	YES	YES	YES	1	NO	YES
31									
32	<i>Corticosteroids for systemic use</i>	YES	NO	YES	YES	YES	10	NO	YES
33									
34	Pharmacological approaches – various								
35									
36	<i>Medical gases - Oxygen</i>	YES	NO	YES	YES	YES	2	NO	YES
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Pharmacological approaches - non-classified medications (i.e. experimental)								
<i>Amino-oxyacetic acid</i>	NO	NO	YES	YES	YES	2	NO	YES
<i>Glutamate</i>	NO	NO	YES	YES	YES	1	NO	YES
<i>Neramexane</i>	NO	NO	YES	YES	YES	6	NO	YES
<i>Nerve growth factor</i>	NO	NO	YES	YES	YES	2	NO	YES
<i>Dextran 40</i>	NO	NO	YES	YES	YES	1	NO	YES
<i>Selurampanel</i>	NO	NO	YES	YES	YES	1	NO	YES
<i>Vestipitant</i>	NO	NO	YES	YES	YES	1	NO	YES
Sound-based interventions								
<i>Acoustic CR Neuromodulation</i>	NO	YES	YES	YES	?	3	YES	YES
<i>Amplification only devices</i>	YES	YES	YES	YES	YES	8	YES	YES
<i>Combination devices (i.e. combined amplification and sound generation)</i>	YES	YES	YES	YES	YES	5	YES	YES
<i>Phase-tailored sound treatment</i>	NO	NO	YES	YES	NO	1	NO	YES
<i>Sound generators only devices (sometimes referred to as 'maskers')</i>	YES	YES	YES	YES	NO	20	YES	YES
<i>Spectrally tailored sound treatment</i>	NO	NO	YES	YES	NO	3	YES	YES
<i>Auditory training</i>	NO	YES	YES	YES	NO	4	NO	YES
Psychology-based interventions								
<i>Cognitive/Behavioural approaches</i>	YES	YES	NO	YES	YES	36	YES	YES
<i>Counselling</i>	YES	YES	NO	YES	NO	3	YES	YES

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

1 2 3 4 5	Various – electrical stimulation Via mastoid bones	NO	NO	YES	YES	NO	1	NO	YES
6	Various – electrical epidural stimulation of the cortex	NO	NO	YES	YES	NO	1	NO	YES
7	Manual physical therapy								
8 9	Cervical Spine Treatment	YES	NO	YES	YES	NO	2	NO	YES
10 11	Myofascial trigger point deactivation	NO	NO	YES	YES	NO	1	NO	YES
12 13	Temporomandibular joint treatment	YES	NO	YES	YES	NO	1	NO	YES
14	Relaxation or stress management								
15 16	Biofeedback/ Neurofeedback	NO	NO	YES	YES	NO	8	NO	YES
17 18	Hypnosis/ hypnotherapy	NO	NO	YES	YES	NO	3	NO	YES
19 20	Relaxation	YES	NO	YES	YES	NO	7	NO	YES
21	Complementary and alternative therapies								
22 23	Acupuncture	NO	NO	YES	YES	YES	26	YES	YES
24 25 26	Dietary supplements and herbal remedies – Alpha lipoic acid	NO	NO	YES	YES	YES	1	YES	YES
27 28 29	Dietary supplements and herbal remedies – Bu-Zhong-Yi-Qi	NO	NO	YES	YES	YES	1	YES	YES
30 31 32	Dietary supplements and herbal remedies – Caffeine	NO	NO	YES	YES	YES	1	YES	YES
33 34 35	Dietary supplements and herbal remedies – Gushen Pian	NO	NO	YES	YES	YES	1	YES	YES

1 2 3 4 5 6 7 8	<i>Dietary supplements and herbal remedies – Hangekobokuto</i>	NO	NO	YES	YES	YES	1	YES	YES
9 10 11 12 13 14	<i>Dietary supplements and herbal remedies – Honeybee larvae</i>	NO	NO	YES	YES	YES	2	YES	YES
15 16 17 18 19 20 21 22 23	<i>Dietary supplements and herbal remedies – Korean Red Ginseng</i>	NO	NO	YES	YES	YES	1	YES	YES
24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	<i>Dietary supplements and herbal remedies – Manganese</i>	NO	NO	YES	YES	YES	1	YES	YES
	<i>Dietary supplements and herbal remedies – Homeopathy</i>	NO	NO	YES	YES	YES	1	YES	YES
	<i>Laser treatment</i>	NO	NO	YES	YES	YES	14	NO	YES
	<i>Ozone</i>	NO	NO	YES	YES	YES	1	NO	YES
	<i>Ultrasound</i>	NO	NO	YES	YES	YES	2	NO	YES
	<i>Vibratory stimulation</i>	NO	NO	YES	YES	YES	2	NO	YES
	<i>Virtual reality</i>	NO	NO	YES	YES	YES	1	NO	YES
	Education and information								
	<i>Education and information</i>	YES	YES	NO	YES	NO	8	NO	YES
	Self-help interventions								
	<i>Support groups</i>	YES	YES	YES	YES	NO	1	NO	YES