



A process for prioritising systematic reviews in tinnitus

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Sereda et al. *Prioritising topics for systematic review*

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

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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
14
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
18
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.

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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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2
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
15
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
22
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).

26
27 59 There is currently no gold standard treatment for tinnitus, rather, various management
28
29 60 strategies are used or have been trialled. Those include education and information, sound-
30
31 61 based interventions, psychology-based interventions, self-help interventions, relaxation
32
33 62 therapy, pharmacology-based interventions, manual physical therapy, magnetic stimulation,
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35 63 electrical stimulation, complementary and alternative therapies, and combination of two or
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37 64 more approaches (complex interventions). Guidelines for the management of tinnitus have
38
39 65 been developed in the USA and Europe (Cima et al., 2019; Fuller et al., 2017a). In the UK,
40
41 66 there are commissioning guidelines for tinnitus services for adults (Department of Health,
42
43 67 2009), and clinical practice guidance for the assessment and management of tinnitus in
44
45 68 children (British Society of Audiology, 2015) A Clinical Knowledge Summary has been
46
47 69 produced by the National Institute for Health and Care Excellence (NICE) and two national
48
49 70 guidelines are in development: the first by NICE; the second by the British Society of
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51 71 Audiology (BSA). NICE has published the scope of the guidelines that are in development
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53 72 (<https://www.nice.org.uk/guidance/gid-ng10077/documents/final-scope>) outlining which

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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
8
9
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**

20
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**

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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.
45
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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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3 95 (<https://ent.cochrane.org/resources/searching-studies/cochrane-ent-trials-register>) using the
4
5 96 following strategy:

6
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
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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51
52 115 ***Population:*** Children and/or adults with subjective tinnitus

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54
55 116 ***Intervention:*** All interventions for subjective tinnitus

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57
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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5
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
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

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

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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)

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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,

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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,
17
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:*
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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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164 forthcoming NICE Guideline.

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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.
- 13
- 14

15 170 Secondary criteria were whether:

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- 17
- 18 171 5. the intervention was already prioritised by healthcare users and healthcare
- 19
- 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
- 32 177 8. there was evidence for variability in clinical practice, within or across countries.
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- 34

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.,

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

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3 189 sensorineural hearing loss and tinnitus) (Bennett et al., 2012), repetitive Transcranial
4
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
15
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
20
21 197 TRT but on inspection did not adhere to the strict protocol described by the developers of
22
23 198 TRT (Jastreboff and Hazell, 2004). Many of these studies observed the underlying principles
24
25 199 of TRT and its scientific rationale which is generally referred to as the neurophysiological
26
27 200 model of tinnitus (Jastreboff, 1990). The authors of the TRT Cochrane review therefore
28
29 201 proposed to write a separate review of these studies which they described as modified TRT.
30
31 202 After discussion it was decided that a single review of both standard (unmodified) TRT and
32
33 203 modified TRT would be more appropriate and a protocol for a review was published (Phillips
34
35 204 and McFerran, 2010b). However, progress on this new review was suspended at the
36
37 205 suggestion of Cochrane. Methods in this protocol were judged as needing updating.
38
39
40 206 The other three published protocols (acupuncture (Li et al., 2016), low-level laser therapy
41
42 207 (Peng et al., 2014), and an overview of systematic reviews of interventions (Maldonado
43
44 208 Fernández et al., 2015) were withdrawn before the reviews were conducted or completed.
45
46
47 209 Eight of the 10 published Cochrane reviews were assessed as having outdated methods by the
48
49 210 Cochrane methodologist (EA). The review of zinc supplementation was judged as up-to-date
50
51 211 and the methods robust (Person et al., 2016). The review of amplification with hearing aids
52
53 212 was judged to have up-to-date methods such that the decision to update would depend on
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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.

7
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
16 219 conference abstracts with no results published (n=70), or required translation for which we
17
18 220 did not have the resources (Chinese, Japanese, Swedish, Spanish; n=15). Nine abstracts/full
19
20 221 texts were not available. An additional 24 records were identified from lists of references of
21
22 222 systematic reviews bringing the total number of records for full text screening and data
23
24 223 charting to 437. Among those, 365 records were identified that were new (not covered in
25
26 224 existing Cochrane reviews) RCTs with published results: PICOS data were extracted from
27
28 225 those records. In addition, 51 unpublished registered randomised trials were identified and
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30 226 data regarding PICOS and trial status were extracted.

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

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41
42 230 ***Education and information***

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45 231 Eight trials were identified that examined information or education.

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47
48 232 ***Sound-based interventions***

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50 233 Forty-three new trials of sound-based interventions were identified. The interventions trialled
51
52 234 included: 1) Amplification only devices (n=8); 2) Sound generator only devices (sometimes
53
54 235 referred to as maskers; n=20); 3) Combination devices (i.e. combined amplification and
55
56 236 sound generators; n=5); 4) Acoustic Coordinated Reset (CR) Neuromodulation (n=3); 5)

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

4
5 238 Auditory training (n=4).

6
7
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.

25
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27
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
32
33 250 forum.

34
35
36
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)

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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).

28
29
30
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)
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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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3 283 (n=14); 4) Ozone (n=1); 5) Ultrasound (n=2); 6) Vibratory stimulation (n=2); and 7) Virtual
4
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
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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,
49
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,
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56 306 Neuromonics) should be excluded. Counselling was defined according to Culley and Bond

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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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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
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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
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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.
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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
46
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
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52 350 and developing clinical practice guidelines for tinnitus. Three high priority reviews are
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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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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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21
22 363 The scoping exercise described here has already resulted in the expedited production of two
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24 364 Cochrane systematic reviews (Sereda et al., 2018; Wegner et al., 2018) in part to inform the
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26 365 NICE guideline on tinnitus which is currently under development. A further three priority
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28 366 reviews are currently in progress (Fuller et al., 2017b; Hoare et al. 2015; and Gingko biloba –
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30 367 protocol in preparation).

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4
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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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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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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
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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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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

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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
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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
24
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.
30
31

33 85 **Scoping review**

34
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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
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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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.

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

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54 116 ***Intervention:*** All interventions for subjective tinnitus

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57 117 ***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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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
21
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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32
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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

38
39 132 populated. When judging whether an existing Cochrane systematic review required updating

40
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

48
49 137 aspects of the systematic reviews were assessed including (1) whether a Preferred Reporting

50
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,

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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->

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- 165 [ng10077/documents/final-scope](#)). This document ~~outlines~~ outlined the proposed
166 contents of the forthcoming NICE Guideline.
- 167 3. there was ‘no recommendation’ or disagreement in recommendations for an
168 intervention within or between current management guidelines
- 169 4. existing Cochrane systematic reviews concluded there was a lack of evidence for an
170 intervention, but additional evidence is now available or if there ~~was~~ is no current
171 Cochrane review.
- 172 Secondary criteria were whether:
- 173 5. the intervention ~~had was~~ already ~~been~~ prioritised by healthcare users and healthcare
174 practitioners in the James Lind Alliance Priority Setting Partnership for tinnitus as a
175 ‘top 10’ treatment uncertainty.
- 176 6. there were sufficient new RCTs for a new or updated review to be meaningful.
- 177 7. interventions were referred to in the tinnitus research network (TINNET) European
178 clinical practice guideline.
- 179 8. there was evidence for variability in clinical practice, within or across countries.

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

184

185 RESULTS

186 Summary of existing Cochrane reviews

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

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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

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2
3 214 ~~Cochrane Library. The interventions evaluated were Tinnitus Retraining Therapy (TRT),~~
4
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~~
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11 218 ~~amplification with hearing aids. A further eight protocols for systematic reviews had been~~
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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
43
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**

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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

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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
9 265 is worth noting that there is a published protocol for a revision of the Cochrane review of
10
11 266 CBT for tinnitus (Fuller et al., 2017a). This review will examine all interventions for tinnitus
12
13 267 that include cognitive, and/or behavioural interventions. Those would include Acceptance
14
15 268 and Commitment Therapy (ACT) and Mindfulness-based therapies, described as different
16
17 269 'waves' of CBT.
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21

22 ***Self-help interventions***

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25 271 One trial was identified that examined a self-help intervention, namely an online discussion
26
27 272 forum.
28
29

30 ***Relaxation therapy***

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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).
36
37

38 ***Pharmacology-based interventions***

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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.
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57 ***Manual physical therapy***

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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***

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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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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***

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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).
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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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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

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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
13
14 361 intervention, education and information only. Antiepileptics met the first two primary criteria
15
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

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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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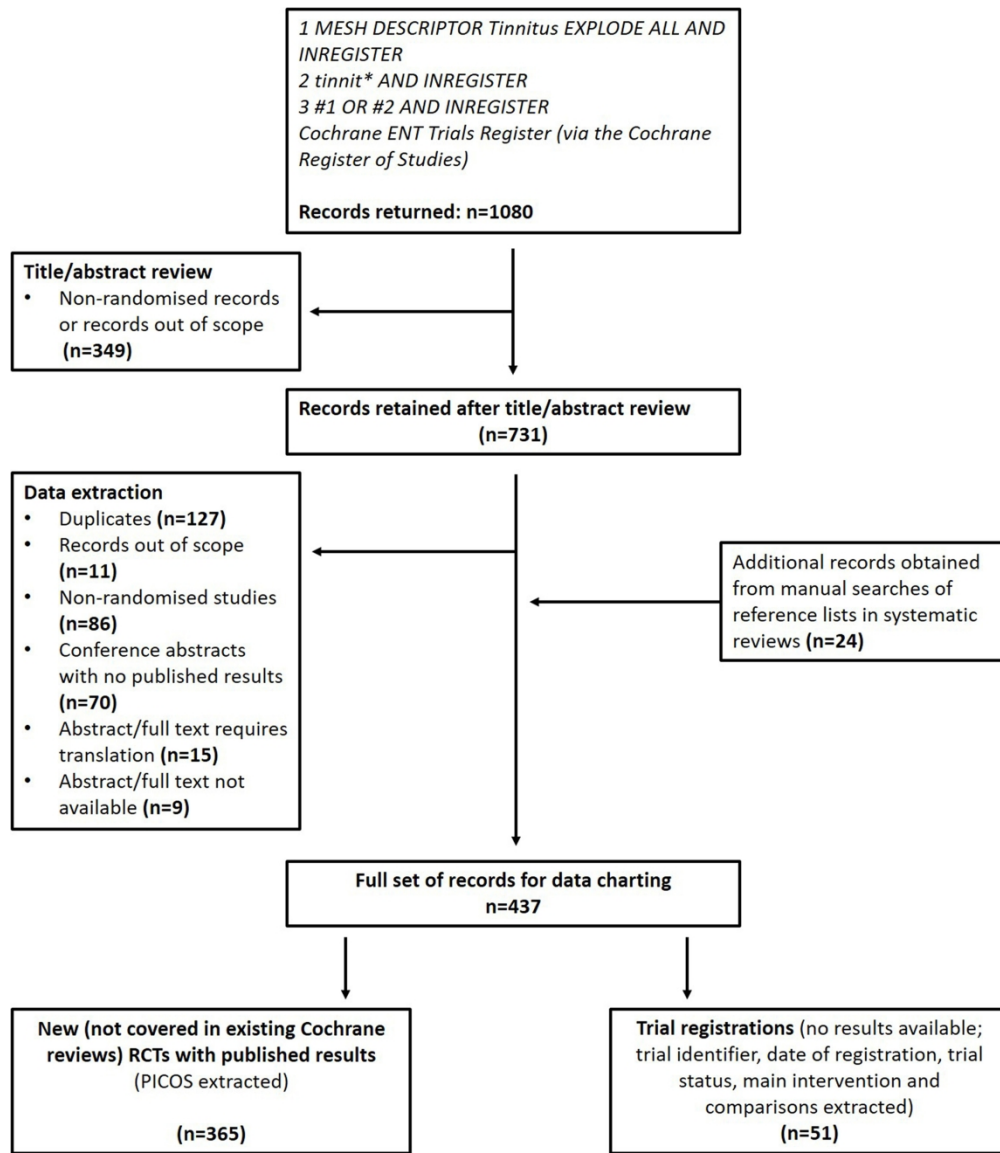


Figure 1. Flow diagram illustrating search strategy and scoping review stages

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 | | | | | | | | |

| | | | | | | | | |
|--|-----|----|-----|-----|-----|----|-----------------------------|-----|
| <i>Antithrombotic agents</i> | YES | NO | YES | YES | YES | 5 | NO | YES |
| <i>Antianemic preparations</i> | NO | NO | YES | YES | YES | 2 | YES Vitamin B12 | YES |
| Pharmacological approaches - Cardiovascular system | | | | | | | | |
| <i>Antiarrhythmics</i> | YES | NO | YES | YES | YES | 11 | NO | YES |
| <i>Peripheral vasodilators</i> | YES | NO | YES | YES | YES | 5 | NO | YES |
| <i>Lipid modifying agents</i> | NO | NO | YES | YES | YES | 1 | NO | YES |
| <i>Other cardiac preparations</i> | YES | NO | YES | YES | YES | 3 | NO | YES |
| Pharmacological approaches - Genito-urinary system and sex hormones | | | | | | | | |
| <i>Uterotonics</i> | NO | NO | YES | YES | YES | 3 | NO | YES |
| <i>Urologicals</i> | NO | NO | YES | YES | YES | 2 | NO | YES |
| Pharmacological approaches - Musculo-skeletal system | | | | | | | | |
| <i>Anti-inflammatory and antirheumatic products</i> | YES | NO | YES | YES | YES | 1 | NO | YES |
| <i>Muscle relaxants</i> | NO | NO | YES | YES | YES | 1 | NO | YES |
| Pharmacological approaches – Nervous system | | | | | | | | |
| <i>Anesthetics - General anesthetics</i> | NO | NO | YES | YES | YES | 4 | NO | YES |
| <i>Anesthetics - Local anesthetics</i> | YES | NO | YES | YES | YES | 18 | NO | YES |
| <i>Antiepileptics</i> | YES | NO | YES | YES | YES | 11 | YES Benzo- diazepines | YES |
| <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 |
| 37 | | | | | | | | | |
| 38 | | | | | | | | | |
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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 |

| | | | | | | | | | |
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| 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 |