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Cognitive behavioural therapy for tinnitus (Protocol)

Fuller T, Cima R, Langguth B, Mazurek B, Waddell A, Hoare DJ, Vlaeyen JWS

Fuller T, Cima R, Langguth B, Mazurek B, Waddell A, Hoare DJ, Vlaeyen JWS.
Cognitive behavioural therapy for tinnitus.
Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD012614.
DOI: 10.1002/14651858.CD012614.

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[Intervention Protocol]

Cognitive behavioural therapy for tinnitus

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Editorial group: Cochrane ENT Group.
Publication status and date: New, published in Issue 4, 2017.

Citation: Fuller T, Cima R, Langguth B, Mazurek B, Waddell A, Hoare DJ, Vlaeyen JWS. Cognitive behavioural therapy for tinnitus. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No.: CD012614. DOI: 10.1002/14651858.CD012614.

ABSTRACT

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

To assess the effects and safety of CBT for tinnitus in adults.

BACKGROUND

The following paragraphs and Description of the condition are based on the Cochrane Review 'Amplification with hearing aids for patients with tinnitus and co-existing hearing loss' and reproduced with permission (Hoare 2014).

Tinnitus is defined as the perception of sound in the absence of a corresponding auditory source (Jastreboff 2004). It is typically described by those who experience it as a ringing, hissing, buzzing or whooshing sound and is thought to result from abnormal neural activity and connectivity in auditory and non-auditory pathways, which is interpreted by the brain as sound (Elgoyhen 2015; Shore 2016). Tinnitus can be either objective or subjective.

Objective tinnitus is estimated to occur in up to 10% of people with tinnitus seeking help (Kircher 2008), and refers to the perception of sound that can also be heard by the examiner (Roberts 2010). Objective forms include heartbeat synchronous pulsatile tinnitus and they usually have a detectable cause such as arteriovenous malformation, carotid stenosis or dissections (Langguth 2013). Specific medication or surgical treatment can lead to the cessation of the tinnitus percept (Kleinjung 2016).

Most commonly, however, tinnitus is subjective, meaning that the sound is only heard by the person experiencing it and no source of the sound can be identified (Jastreboff 1988). Subjective tinnitus (the focus of this review) is estimated to affect up to 21% of the general adult population, increasing to as many as 30% of adults over 50 years of age (Davis 2000; Gallus 2015; Kim 2015). It can be experienced acutely, recovering spontaneously within minutes to weeks. However, it can become chronic and is unlikely to resolve spontaneously when experienced for three months or more (Hahn 2008; Hall 2011; Rief 2005). In 1% to 3% of the population tinnitus causes severe problems with daily life functioning (Davis 2000; Kim 2015). Although a range of psychological, sound, electrical and electromagnetic therapies have been developed, currently there is no reliable cure for subjective tinnitus.

In England alone there are an estimated ¾ million General Practitioner consultations every year where the primary complaint is tinnitus (El-Shunnar 2011), equating to a major burden on healthcare services. For many people tinnitus is persistent and troublesome, and has disabling effects such as insomnia, difficulty concentrating, difficulties in communication and social interaction, and negative emotional responses such as anxiety and depression (Andersson 2009; Cima 2011b; Crönlein 2007; Langguth 2011; Marciano 2003; Zirke 2013a; Zirke 2013b). In approximately 90% of cases, chronic tinnitus is co-morbid with some degree of hearing loss, which may confound these disabling effects (Fowler 1944; Sanchez 2002). An important implication of this in clinical research is that outcome measures need to distinguish benefits specific to the tinnitus signal itself and related aspects such as impairments in communication, emotional processing and social interaction, which all play a relevant role in quality of life.

For the purposes of this review we will use the term 'tinnitus reactivity' as a collective term for the cognitive, emotional and behavioural consequences/sequelae that people living with chronic tinnitus experience. Additionally, unless otherwise noted, we will refer to subjective tinnitus simply as tinnitus.

Description of the condition

Pathophysiology

Most people with chronic tinnitus have some degree of hearing loss (Ratnayake 2009), and the prevalence of tinnitus increases with greater hearing loss (Han 2009; Martines 2010). Converging evidence from animal models and studies of human tinnitus sufferers indicates that, while cochlear damage is a trigger, most cases of tinnitus are generated by changes that take place in central auditory pathways when auditory neurons lose their input from the ear (Noreña 2011). Forms of neural plasticity underlie these neural changes, which include: increased spontaneous activity and neural gain in deafferented central auditory structures; increased synchronous activity in these structures; and changes in network behaviour in non-auditory brain regions. These changes have been detected by functional imaging of individuals with tinnitus and corroborated by animal investigations (Eggermont 2014; Elgoyhen 2015). (Additional detail is provided in Appendix 1).

A complication in understanding the pathophysiology of tinnitus is that not all people with hearing loss have tinnitus and not all people with tinnitus have a clinically significant hearing loss. Other variables, such as the profile of a person's hearing loss, may account for differences in their tinnitus report. For example, König 2006 found that the maximum slope within audiograms was higher in people with tinnitus than in people with hearing loss who do not have tinnitus, despite the 'non-tinnitus' group having the greater mean hearing loss. Also the additional involvement of non-auditory areas of the brain, particularly areas associated with awareness and salience detection, can explain why some people with hearing loss develop tinnitus whereas others do not (de Ridder 2011; de Ridder 2014).

Whether tinnitus is perceived as bothersome or not may be related to the additional involvement of emotion processing areas (Rauschecker 2010; Schecklmann 2013; Vanneste 2012). Accordingly, some models have proposed that tinnitus reflects "an emergent property of multiple parallel dynamically changing and partially overlapping sub-networks". This suggests that various brain networks associated with memory and emotional processing are involved in tinnitus and that the degree of involvement of the different networks reflects the variable aspects of an individual's tinnitus (de Ridder 2011; de Ridder 2014; Elgoyhen 2015).

Psychological models of tinnitus

In addition to the physiological data and models of tinnitus, psychological models have been developed to explain how and why some people experience tinnitus reactivity whereby it becomes aversive. Psychological models of tinnitus include those developed by Hallam, which applies the concept of habituation (Hallam 1984); Jastreboff, whose model features classical conditioning mechanisms (Jastreboff 1988; Jastreboff 1990); and the cognitive behavioural models of McKenna 2014, Cima 2011b and Kleinstauber 2013 (Appendix 2). These psychological models underpin the rationale and development of cognitive behavioural interventions for aversive tinnitus reactivity.

Diagnosis and clinical management of tinnitus

There is no universal internationally established standard procedure for the diagnosis or management of tinnitus. However, common across the (few) published practice guidelines is the use or recommendation of self-report questionnaires to assess tinnitus and its impact on patients by measuring severity, quality of life, depression or anxiety (Fuller in press). Psychoacoustic measures of tinnitus (pitch, loudness, minimum masking level) are also used in patient assessment but do not correlate well with self-reported measures of tinnitus annoyance (Hiller 2006). Instead they represent measurements of tinnitus that can be useful in patient counselling (Henry 2004) by, for example, demonstrating changes (or stability) in the individual's perception of the tinnitus over time (Department of Health 2009). No objective measures of tinnitus currently exist and so researchers and clinicians are reliant upon patient self-report measures (usually questionnaires with Likert-type or visual analogue scales) to record any changes in tinnitus reactivity or other general health effects of therapy (Appendix 3).

The previous Cochrane Review of cognitive behavioural therapy for tinnitus used self-reported, subjective tinnitus loudness as the primary outcome measure (Martinez-Devesa 2010). That review and others like it have consistently reported that there are generally weak (if any) effects of the intervention on the level of perceived loudness of the tinnitus (Andersson 1999; Martinez-Devesa

2010). Additionally, concerns have been raised about what is actually being measured when people are asked to rate the subjective loudness of their tinnitus (McKenna 2014).

Clinical management strategies include education and/or counselling, relaxation therapy, tinnitus retraining therapy (TRT), cognitive behavioural therapies (CBT) and sound enrichment using ear-level sound generators or hearing aids (Henry 2005). In addition, electrical and neurostimulation, as well as drug therapies aimed at treating tinnitus directly, or managing co-morbid symptoms such as insomnia, anxiety or depression, have been tested. The effects of these management options are variable, they have inconclusive outcomes and some have risks or adverse effects (Dobie 1999; Hoare 2011a; Hoare 2011b; Hobson 2012; Langguth 2013; Martinez-Devesa 2010; Phillips 2010).

Description of the intervention

Cognitive behavioural therapy (CBT) is an inclusive term that features and combines numerous psychological interventions that were developed and evolved from cognitive and behavioural therapies respectively. CBT for tinnitus aims primarily to reduce the reactivity associated with tinnitus, rather than the perceived loudness.

Behavioural therapies (e.g. behavioural activation, exposure, relaxation) aim to help patients overrule learned associations between tinnitus and counter-productive responses (e.g. avoiding tinnitus-increasing activities). Cognitive therapies, on the other hand, focus on the relationship between thoughts and emotions (Ellis 1977), and apply a process of identification and modification of errors in thought processing of experiences (Beck 1979). Combined, the behavioural and cognitive theories have produced a range of intervention components designed to address the dysfunctional thought processes, behavioural and emotional responses that maintain aversive reactivity.

As discussed by Cima 2014, cognitive behavioural interventions such as mindfulness-based stress reduction (also known as 'mindfulness'; Kabat-Zinn 1982) and acceptance and commitment therapy (ACT; Hayes 1999) have been developed and applied to the treatment of tinnitus reactivity (e.g. Hesser 2009; Philippot 2012). For the purposes of this review, we will not make distinctions between whether an intervention is 'first', 'second' or 'third wave' CBT. Instead, we will treat ACT and mindfulness interventions as CBT and in the course of data extraction we will identify components/elements within all interventions as behavioural, cognitive or a combination (i.e. CBT).

Interventions described or labelled as 'CBT' cannot be assumed to be equivalent homogenous entities. Even if CBT interventions comprise the same elements they might vary with regard to: the mode of delivery of the intervention (e.g. face-to-face, mediated via telephone, Internet); the frequency of sessions (e.g. daily, weekly, fortnightly); the length of sessions; the duration of the intervention; who delivers the CBT (e.g. psychologist, social worker, nurse, computer program); the setting in which the treatment is delivered (e.g. hospital, health centre, private clinic); and whether the therapy is delivered in a group or individual format.

The previous Cochrane Review of CBT for tinnitus found that there were no reported adverse events in the included trials (Martinez-Devesa 2010). It is, however, conceivable that people might experience a deterioration in their mood during the course of CBT, due to the often challenging nature of the therapy or the distress arising as a result of changes in cognitive and emotional mechanisms. It is also possible that adverse events were not reported by the authors of studies included in the review, as this is a common occurrence in trials (Pitrou 2009).

How the intervention might work

Since a growing body of evidence suggests that tinnitus reactivity depends more on psychological factors than acoustic properties (Cima 2014; Milerova 2013), psychological therapies have been widely used for tinnitus treatment.

Cognitive strategies are based on the idea that negatively biased interpretations or thoughts about specific events or experiences, such as hearing tinnitus, produce a dysfunctional emotional and/or behavioural response (Beck 1979; Ellis 1977). Thus, cognitive strategies are thought to work by identifying any biased or irrational thinking styles (such as catastrophising), then challenging, modifying and/or replacing them with alternative and more realistic beliefs that lead to a more adaptive response.

A behavioural intervention such as an exposure therapy might be utilised to decrease the impact of tinnitus on daily life. Exposure to the tinnitus sound is thought to work through a process of extinction learning and generalisation. That is, a person learns that the tinnitus sound is no longer indicative of being emotionally aroused or in a distressed state and applies this new knowledge to situations beyond those learned in the therapeutic setting. In daily life this might mean a person re-engages in activities that they previously avoided for fear that the tinnitus would deteriorate.

Individually, cognitive and behavioural therapy components are hypothesised to have specific effects. For example, education regarding the physiology and pathophysiology of hearing and tinnitus are thought to provide a foundation on which patients can begin to understand that tinnitus is not a harmful symptom in its own right and hence nothing, logically at least, to be afraid of. Cognitive behavioural approaches to tinnitus therapy are therefore hypothesised to affect a reduction in aversive tinnitus reactivity though the summed or synergistic effects of the specific intervention components included in an individual therapy. Further, it is hypothesised that this has a consequent effect of reducing generalised anxiety or depression where it is co-morbid, and generally improving self-reported quality of life.

To date there has been little detailed research examining precisely when therapeutic change occurs during the course of CBT treat-

ments, but they have been reported to be effective over at least a 12-month period (e.g. Cima 2012).

Why it is important to do this review

This review will include recent randomised controlled trials of CBT for tinnitus that were not included in previous meta-analyses or recent reviews. The most recently published review of CBT interventions for tinnitus was a historical and narrative overview in which a range of study designs in addition to RCTs were included, but one in which neither a risk of bias assessment was undertaken nor a meta-analysis conducted (Cima 2014). These methodological issues make it harder to draw conclusions about the strength of any treatment effects and risks of bias in the evidence included in the narrative synthesis.

A second reason is that it is also important to address new questions that will inform decisions about service provision, as this has particular relevance for the policy-makers and agencies involved in the funding of treatment (e.g. insurance companies). CBT for tinnitus is generally well received by patients and is potentially a cost-effective means for reducing the reactivity (Maes 2014), but it would also be informative to compare the effectiveness of CBT delivered in group and individual formats and CBT performed by psychologists compared with other health professionals.

A new review and meta-analysis of CBT for tinnitus will also inform the development of European clinical treatment guidelines, which is currently being undertaken (Tinnet 2016).

Finally, since the previous version of the Cochrane Review of CBT for tinnitus was published (Martinez-Devesa 2010), Cochrane standards for the conduct of intervention reviews have been revised (Higgins 2013; Higgins 2016). A new review will not only include recent randomised controlled trials, but will also comply with the new standards in ways that the previous version of the review now does not. For example, a specific, a priori description of how heterogeneity between studies included in the review will be identified and assessed is clearly described.

In summary, this review will synthesise the latest evidence related to CBT for tinnitus, which will help inform decisions on whether CBT for tinnitus is effective at reducing aversive tinnitus reactivity.

OBJECTIVES

To assess the effects and safety of CBT for tinnitus in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (including cluster-randomised). If studies that use a cross-over design are included, we will only include data from the first treatment phase. Quasi-randomised controlled studies will not be included.

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

Types of participants

Participants will be at least 18 years of age with tinnitus as the primary reason for seeking treatment.

In the event that studies include an age range of participants below 18 years (e.g. 16 to 21 years), they will be included if the mean age is 18 years or above.

Types of interventions

The primary intervention of interest is CBT. For the purposes of this review we will include studies that also describe CBT interventions that apparently only use cognitive or behavioural elements. Interventions such as ACT and mindfulness will also be included but simply considered as types of CBT.

For the purposes of determining similarities for subgroup analysis, we will contact authors of studies that examine the effectiveness of an apparently 'pure' cognitive or behavioural interventions and request treatment manuals or protocols. Two authors will then independently review the intervention manual classifying treatment elements as either cognitive or behavioural. Based on results from a review of treatment components used in psychological therapy for people with tinnitus (Thompson 2016) and the behaviour change taxonomy (Michie 2013), we will classify interventions as either 'cognitive only', 'behavioural only' or 'CBT'. In the event that the review authors differ in their judgements, a third review author will act as an arbiter.

We will stratify studies into four comparisons:

- CBT versus no intervention/waiting list control;
- CBT versus usual audiological care (tinnitus education and rehabilitation for hearing loss);
- CBT versus TRT (directive counselling and bilateral masking);
- CBT versus other experimental control (pooled if using the same experimental control). Other experimental controls may include transcranial magnetic stimulation, electrical or electromagnetic stimulation therapy and bio- neuro-feedback.

Types of outcome measures

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

Primary outcomes

- Tinnitus reactivity as measured by validated tinnitus-specific health-related quality of life multi-item questionnaires identified in a systematic review of outcome instruments used in trials of interventions for tinnitus (Hall 2016). These include:
    - Tinnitus Questionnaire;
    - Tinnitus Functional Index;
    - Tinnitus Handicap Inventory;
    - Tinnitus Handicap Questionnaire;
    - Tinnitus Reaction Questionnaire;
    - Tinnitus Severity Scale;
    - Tinnitus Disability Index.

(For references associated with the outcome measures see Appendix 4).

If a study uses multiple measures of tinnitus reactivity we will apply the following as a hierarchy of the outcome measures based on their known psychometric validity (Fackrell 2014): Tinnitus Functional Index, Tinnitus Handicap Inventory, Tinnitus Handicap Questionnaire, Tinnitus Questionnaire, Tinnitus Reaction Questionnaire, Tinnitus Disability Index, Tinnitus Severity Scale and then other tinnitus-specific questionnaires. Invariably these questionnaires show good convergent validity.

- Significant adverse effect: self-harm, suicide, suicide attempt, suicidal crisis, severe symptom exacerbation.

Secondary outcomes

- Generalised depression as measured by validated questionnaires, such as the Beck Depression Inventory II (Beck 1996), the depression scale of the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983), and the Hamilton Rating Scale for Depression (Hamilton 1960).
- Generalised anxiety as measured by a validated scale, for example, the anxiety scale of the HADS or Beck Anxiety Inventory (Beck 1988) or the Anxiety Sensitivity Index (Reiss 1986).
- Health-related quality of life as measured by a validated scale, for example, the Short-Form 36 (Hays 1993), WHOQoL-BREF (Skevington 2004), and other WHOQoL versions, Health Utilities Index (Furlong 2001).
- Negatively biased interpretations of tinnitus as measured by a validated scale, such as the Tinnitus Catastrophizing Scale (Cima 2011b), the Fear of Tinnitus Questionnaire (Cima 2011b), and the Tinnitus Fear and Avoidance Scale (Kleinstauber 2013).
- Other adverse effects: acute emotional discomfort.

We will measure outcome at treatment end (typically six to eight weeks) and at long-term follow-up (6 and 12 months).

Search methods for identification of studies

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

Electronic searches

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

- the Cochrane Register of Studies ENT Trials Register (search to date);
- Cochrane Register of Studies Online (search to date);
- Ovid MEDLINE (1946 to date);
    - Ovid MEDLINE (In-Process & Other Non-Indexed Citations);
    - PubMed (as a top up to searches in Ovid MEDLINE);
- Ovid EMBASE (1974 to date);
- EBSCO CINAHL (1982 to date);
- Ovid AMED (1985 to date);
- Ovid PsycINFO (1806 to date);
- Ovid CAB abstracts (1910 to date);
- LILACS (search to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date);
- ISRCTN, www.isrctn.com (search to date);
- Google Scholar (search to date).

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL (Appendix 5). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b (Higgins 2011).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE, the *Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

TF and RC will independently screen titles and abstracts from the search results for eligible studies. If there are disagreements at this screening stage, we will obtain copies of the full-text articles and examine them closely for eligibility. For all disagreements over full-text articles being assessed for inclusion, a third review author will be consulted as an arbiter.

We will record and present the flow of study identification and selection in the form of a PRISMA flow chart (Moher 2009).

Data extraction and management

TF will co-ordinate the retrieval of full-text articles as well as the management and extraction of all data. Two of TF, RC or BM will independently extract data from the included studies into standardised data forms based on a generic form developed by the Cochrane ENT editorial group. In the event that one of the review authors is the author of an included study he or she will not extract data from the study. Where relevant, review authors will be required to copy and paste verbatim text from included articles into the data extraction form. Any disagreements in the data extraction will first be addressed through discussion between the review authors involved. If that does not lead to agreement, a third review author will be consulted as an arbiter. In the event of information from an included study not being reported in adequate detail to enable decisions about inclusion or exclusion, we will contact the authors to request the provision of additional information.

Data extraction will include information on the following: details of the source, eligibility, methods, participants, intervention treatment elements, outcome measures at baseline (or pre-test) and other time points reported in the respective studies, results including estimates of effects and confidence intervals, details of the funding source, key conclusions from the authors, comments from the review authors especially with regard to any differences between protocols and study reports, details of any correspondence required and any references to other relevant studies. Further details of the data to be extracted for intervention reviews are specified in table 7.2 of the *Cochrane Handbook for Systematic of Interventions* (Higgins 2011).

At the completion of data collection and once there is agreement on the data set that has been extracted, we will enter data into Review Manager 5.3 (RevMan 2014).

Assessment of risk of bias in included studies

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

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. In the event of disagreement between assessors of risk of bias, we will discuss the rationale for the respective judgements in an effort to resolve the differences. If this does not lead to agreement, a third review author will act as an arbiter.

Measures of treatment effect

We will analyse ordinal data as if it were continuous data and use standardised mean differences (SMD) and Cohen's d effect size measurement to estimate treatment effects for measures of tinnitus reactivity and other continuous measures of secondary outcomes. If feasible, we will also pool data from the same scale and use mean differences (MD). In the scenario where dichotomous data are reported we will analyse the data using risk ratios (RR) with 95% confidence intervals (95% CIs).

Unit of analysis issues

We do not anticipate that researchers conducting RCTs of CBT for tinnitus will employ a cross-over design (i.e. where patients/participants receive both the experimental and control interventions) due to the carry over effects that would be expected from a CBT intervention. However, if an included study uses a cross-over design individual participant data constituting the unit of analysis from the first treatment phase would be included in a meta-analysis.

If any included study uses a cluster-randomised design we will choose statistical methods in consultation with a statistician and following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* to "extract an estimate of the required effect measure from an analysis that accounts for the cluster design" using an odds ratio with confidence interval or generalised estimating equations (Higgins 2011). Also as specified we will use the inverse variance method to meta-analyse effect estimates and standard errors so that the clustered nature of the data is taken into consideration (Higgins 2011).

Dealing with missing data

Whenever possible we will attempt to contact the investigators to request missing data relating to, for example, study characteristics, outcome measures, or how many patients dropped out or were

included in the analysis. In relation to missing information about dropout or numbers included in the analysis, if we do not receive a response from the authors, we will conduct the analysis using a conservative approach and assume that the missing patients' data indicate no effect of/from the intervention. We will undertake a sensitivity analysis to examine the effect of this assumption by comparing the results with what would happen if the missing patients had the best possible outcome.

Where there are missing standard deviations for continuous data, we will use methods to estimate these using confidence intervals, standard errors, t, P or F values where reported.

We will record attempts to contact authors for missing data and responses (or otherwise) and, along with consideration of the potential impact of the missing data, report this in the Discussion section of the review.

Assessment of heterogeneity

We will investigate clinical heterogeneity with regard to: components of the interventions, mode of delivery, level of action, who delivers the CBT and the type of intervention used in the control condition. We will assess methodological heterogeneity according to study design and risk of bias (i.e. randomisation, blinding of outcome assessment, losses to follow-up).

We will assess the degree of statistical heterogeneity that exists across studies using the I^2 statistic and we will use the following from the *Cochrane Handbook for Systematic Reviews of Interventions* as a guide for interpretation (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If we are able to include 10 or more studies, we will examine reporting bias through the creation of a funnel plot.

Data synthesis

In the event of being able to conduct meta-analyses, we will use a random-effects model as we expect that there will be differences between the study populations and methods used. We will subsequently conduct a sensitivity analysis using a fixed-effect model.

First we will pool all studies if there is sufficient similarity between them with regard to: outcome (good convergent validity), level of action (i.e. individual or group therapy) and mode of delivery (i.e. in person, face-to-face or online). We assume that the included studies will all be RCTs, intervention studies and include a patient population.

We will stratify studies into four comparisons:

- CBT versus no intervention/waiting list control;
- CBT versus usual audiological care (tinnitus education and rehabilitation for hearing loss);
- CBT versus TRT (directive counselling and bilateral masking);
- CBT versus other experimental control (pooled if using the same experimental control). Other experimental controls may include transcranial magnetic stimulation, electrical or electromagnetic stimulation therapy or bio- neuro-feedback.

The intention is to pool the results of the CBT treatments. However, if CBT treatment protocols are found to differ extensively synthesis may not be valid and we will conduct clustered analyses. We will not pool studies if they differ on multiple clinical (intervention type, participant characteristics, mode of delivery, level of action, outcome) or methodological (study design, comparator) criteria relevant for a specific question the review addresses. Similarly, if there are indications of significant statistical heterogeneity (i.e. the I^2 statistic is > 30%, the Chi^2 value is greater than the degrees of freedom and/or the confidence intervals of the included studies do not show overlap), we will not pool studies and instead we will describe the findings in a narrative form.

Subgroup analysis and investigation of heterogeneity

We plan to conduct subgroup analyses for the primary outcome of tinnitus reactivity for the following:

- Studies by types of therapy: 'cognitive only', 'behavioural only', 'cognitive and behavioural only'.
- Studies by modes of delivery: 'face-to-face' or 'online CBT'.
- Studies by unit of delivery: 'individual patient therapy' or 'group therapy'.
- Study or patient groups by who delivers CBT; 'psychologists' or 'psychiatrists' or 'audiologists' or other therapists or clinicians.
- Studies by whether participants are included/excluded according to their hearing status: 'hearing loss was an exclusion criterion' or 'hearing loss was not an exclusion criterion'.

Sensitivity analysis

We plan to conduct the following sensitivity analyses to examine the role of:

- meta-analysis using random-effects and fixed-effect models respectively;
- including or excluding studies at high risk of bias for incomplete outcome data.

GRADE and 'Summary of findings' table

We will use the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings:

high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

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

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

We will include 'Summary of findings' tables, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will present a 'Summary of findings' table for CBT compared with no intervention/waiting list control, usual audiological care, TRT and other control interventions. We will report the following outcomes in the 'Summary of findings' tables: aversive tinnitus reactivity, adverse events, quality of life, depression, anxiety and negatively biased interpretations of tinnitus.

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

We would like to also specifically acknowledge Jenny Bellorini and Samantha Faulkner for practical assistance and preparing the search strategy respectively.

Thomas Fuller was supported by SWOL Limburgs Fonds voor Revalidatie and the Netherlands Organisation for Health Research and Development (ZonMW), Research programme: Health Care Efficiency, Subprogramme: Effects & Costs, Grant number: 945-07-715.

Rilana Cima received funding from the Innovational Research Incentives Scheme Veni, from the Netherlands Organisation for Scientific Research (NWO).

Derek J Hoare is funded through the National Institute for Health Research (NIHR) Biomedical Research Programme. The view expressed are those of the author and not necessarily those of the NIHR, the NHS or the Department of Health.

Johan WS Vlaeyen received funding from the Research Foundation, Flanders FWO, Belgium (Fonds Wetenschappelijk Onderzoek Vlaanderen) and the Netherlands Organisation for Health Research and Development (ZonMW).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Pathophysiology of tinnitus

In the central auditory system, tinnitus-related alterations have been described along the whole central auditory pathway including the dorsal cochlear nucleus (Middleton 2011; Pilati 2012), the inferior colliculus (Dong 2010; Mulders 2010), and the auditory and non-auditory cortex (for review see Elgoyhen 2015). There is a strong rationale that these structural and functional alterations are a direct consequence of maladaptive neuroplastic responses to hearing loss (Møller 2000; Mühlnickel 1998), or to altered somatosensory input from the face or the neck (Shore 2016). Presumably sensory deafferentation triggers a release from inhibition in the central auditory system resulting in spontaneous hyperactivity and increased spontaneous synchronous activity within the central neuronal networks involved in sound processing (Dietrich 2001; Eggermont 2004; Rauschecker 1999; Schaette 2011; Seki 2003; Tass 2012; Weisz 2005). Another physiological change thought to be related to tinnitus generation is a process of functional reorganisation. This amounts to a change in the response properties of neurons within the primary auditory cortex to external sounds. This effect is well demonstrated physiologically in animal models of hearing loss (Engineer 2011; Noreña 2005). Evidence in humans, however, is limited to behavioural evidence of cortical reorganisation after hearing loss, demonstrating improved frequency discrimination ability at the audiometric edge (Kluk 2006; McDermott 1998; Moore 2009; Thai-Van 2002; Thai-Van 2003), although Buss 1998 did not find this effect. Imaging studies in tinnitus patients without hearing loss as shown in a normal audiogram did not demonstrate functional reorganisation of the brain's auditory system macroscopically altered tonotopic organisation (Langers 2012), indicating that altered tonotopic organisation is rather a consequence of hearing loss and not causally related to tinnitus. This indicates that such reorganisation is a consequence of hearing loss, but is not sufficient to cause tinnitus.

Appendix 2. Psychological models of tinnitus reactivity

Several influential models have been proposed to explain the development and maintenance of aversive reactivity associated with chronic subjective tinnitus. Each of the models are briefly described here as they underlie the development of and rationale for applying cognitive behavioural therapy to the treatment of aversive tinnitus reactivity.

The concept of habituation - a process whereby reaction(s) decrease in response to repeated presentation of a stimulus (Bouton 2007) - was first applied in 1984 by Hallam and colleagues to explain reduction in tinnitus reactivity over time. They proposed that for most people repeated perception of the tinnitus sound led them to learn that the stimulus was not worthy of attentional resources (Hallam 1984). However, aversive tinnitus-related reactivity occurs when there are failures in these attentional processes that might especially happen at times of stress and high arousal, which put strain on cognitive resources (Mazurek 2015). Operant conditioning (Skinner 1938), which attributes importance to the consequences of actions, was later included in the model to account for learning mechanisms and avoidant behaviours (Kroener-Herwig 2003). The difficulty for the person arises though when significant or continuous resources (cognitive or otherwise) are needed to avoid the tinnitus to experience relief. To treat tinnitus reactivity (or facilitate habituation to tinnitus), it was recommended that stress levels and central nervous system arousal levels should be reduced in order to change the meaning of the tinnitus signal for the patient (McKenna 2004). To date there is mixed evidence in support of the habituation model (Baguley 2013).

Jastreboff expanded this model by postulating that the association between tinnitus and an aversive emotional state emerges through classical conditioning mechanisms (Jastreboff 1988; Jastreboff 1990). Classical (or Pavlovian) conditioning refers to a process whereby a person learns a relationship between the two stimuli, a neutral one (conditioned stimulus) and a biologically relevant one (unconditioned stimulus) (Pavlov 1927). Subsequent presentation of either will activate the representation of the biologically relevant one and elicit a conditioned response. While Jastreboff described how an association developed between the tinnitus perception and an aversive emotional state, it was not clearly specified what the unconditioned stimulus, conditioned stimulus and conditioned responses respectively were (Baguley 2013). Regardless, to counter the effect, treatment should aim to break the negative association with the tinnitus percept by using directive cognitive therapy and sound therapy (Jastreboff 1993; Jastreboff 2004).

More recently a cognitive model (McKenna 2014), and cognitive-behavioural (i.e. fear avoidance) model (Cima 2011b; Kleinstauber 2013; Lethem 1983; Vlaeyen 2000; Vlaeyen 2012), have been applied to tinnitus. The cognitive model stresses the importance of primary and secondary cognitive appraisals and the effect on attentional processes (McKenna 2014). The negative evaluation of the tinnitus can be viewed as being comprised of primary and secondary appraisals. That is, a person might initially appraise the tinnitus as being threatening to their health, and then make a secondary appraisal of their (in)ability to control it. The fear avoidance model of tinnitus shares features with both the neurophysiological and the cognitive model including attributing a fundamental role to the negative evaluation of tinnitus. The fear avoidance model offers predictions about behavioural factors (e.g. safety behaviours) in the

maintenance of chronic tinnitus reactivity. It is proposed that regardless of the cause of the tinnitus, once it is detected, attention, cognitive appraisals and emotional reactions elicit behavioural responses, which are relieving in the short term but paradoxically lead to severe impairment in the long term.

In the fear avoidance model, the role of fear reactions and safety behaviours is purported to be the key mechanism in the maintenance of chronic tinnitus suffering (Cima 2011b; Kleinstauber 2013). Its central tenet is that the main reactions to tinnitus depend on the initial response. In case of misinterpretations, increased threat value will be associated with tinnitus. That is to say, negative autonomic psychophysiological reactivity may lead to catastrophic (mis)interpretations (i.e. a bias towards misinterpreting the tinnitus as something extremely harmful). Fear responses, such as avoidance and escape tendencies, will in turn lead to task-interference, depression, inactivity and ultimately to severe impairment in daily life (Cima 2011a; Cima 2011b). These fear behaviours are reinforced since they offer relief by reducing fear and acute reactivity in the short term, but unfortunately prolong fear-avoidance responsiveness and therefore impairment in the long term.

Although these psychological models slightly differ in their main premise and in some of the terminology used, they all identify mechanisms, either of a cognitive and/or behavioural nature, which have been targeted in therapy to reduce reactivity.

Appendix 3. Tinnitus measurement tools

There are numerous tools used for tinnitus evaluation including the **Tinnitus Questionnaire** (TQ) (Hallam 1988), the **Tinnitus Reaction Questionnaire** (TRQ) (Wilson 1991), the **Tinnitus Functional Index** (TFI) (Meikle 2012) and the **Tinnitus Handicap Inventory** (THI) (Newman 1996). For a discussion of the development and validity of questionnaires for measuring reactivity and interference associated with tinnitus, see Fackrell 2014.

For illustrative purposes, the THI is presented below.

The THI is a self-administered tool to measure the impact of the tinnitus in daily life (Newman 1996). It consists of 25 items that may be answered yes (four points), sometimes (two points) or no (zero points), summing up a total of 100 points, with higher scores corresponding to a higher handicap. The items are divided into three subscales:

- The functional subscale (F) (11 items) encompasses role limitations in the areas of mental functioning, social/occupational functioning and physical functioning.
- The emotional subscale (E) (nine items) includes items addressing affective responses to tinnitus (anger, frustration, irritability, depression).
- The catastrophic subscale (C) (five items) reflects patients' desperation, inability to escape from tinnitus, perception of having a terrible disease, lack of control and inability to cope.

1. Because of your tinnitus is it difficult for you to concentrate? (F)
2. Does the loudness of your tinnitus make it difficult for you to hear people? (F)
3. Does your tinnitus make you angry? (E)
4. Does your tinnitus make you confused? (F)
5. Because of your tinnitus are you desperate? (C)
6. Do you complain a great deal about your tinnitus? (E)
7. Because of your tinnitus do you have trouble falling asleep at night? (F)
8. Do you feel as though you cannot escape from your tinnitus? (C)
9. Does your tinnitus interfere with your ability to enjoy social activities (such as going out to dinner, to the cinema)? (F)
10. Because of your tinnitus do you feel frustrated? (E)
11. Because of your tinnitus do you feel that you have a terrible disease? (C)
12. Does your tinnitus make it difficult to enjoy life? (F)
13. Does your tinnitus interfere with your job or household responsibilities? (F)
14. Because of your tinnitus do you find that you are often irritable? (F)
15. Because of your tinnitus is it difficult for you to read? (F)
16. Does your tinnitus make you upset? (E)
17. Do you feel that your tinnitus has placed stress on your relationships with members of your family and friends? (E)
18. Do you find it difficult to focus your attention away from your tinnitus and on to other things? (F)
19. Do you feel that you have no control over your tinnitus? (C)
20. Because of your tinnitus do you often feel tired? (F)
21. Because of your tinnitus do you feel depressed? (E)
22. Does your tinnitus make you feel anxious? (E)

23. Do you feel you can no longer cope with your tinnitus? (C)
24. Does your tinnitus get worse when you are under stress? (F)
25. Does your tinnitus make you feel insecure? (E)

According to the score, tinnitus can be classified into five categories:
Category 1: 0 to 16. Slight (only heard in quiet environments).
Category 2: 18 to 36. Mild (easily masked by environmental sounds and easily forgotten with activities).
Category 3: 38 to 56. Moderate (noticed in the presence of background noise, though daily activities can still be performed).
Category 4: 58 to 76. Severe (almost always heard, leads to disturbed sleep patterns and can interfere with daily activities).
Category 5: 78 to 100. Catastrophic (always heard, disturbed sleep patterns, difficulty with any activities).

Appendix 4. Outcome measures and citations

- Tinnitus Questionnaire (Hallam 1988; Hallam 2008).
- German version of Tinnitus Questionnaire (Goebel 1994).
- Tinnitus Functional Index (Meikle 2012).
- Tinnitus Handicap Inventory (Newman 1996).
- Tinnitus Handicap Questionnaire (Kuk 1990).
- Tinnitus Reaction Questionnaire (Wilson 1991).
- Tinnitus Severity Scale (Sweetow 1990).
- Tinnitus Disability Index (Cima 2011a).

Appendix 5. CENTRAL search strategy

#1 MeSH descriptor: [Tinnitus] explode all trees
#2 (tinnit*):ti,ab,kw
#3 #1 or #2
#4 MeSH descriptor: [Behavior Therapy] explode all trees
#5 MeSH descriptor: [Adaptation, Psychological] explode all trees
#6 MeSH descriptor: [Meditation] explode all trees
#7 (CBT or ACT or mindfulness or MBTR or MBSR or MBTSR or psychoeducation or iACT or iCBT or GCBT):ti,ab,kw
#8 ((cogniti* or relaxation or acceptance or commitment or adaptation) near (therap* or behavior* or behaviour* or strateg* or intervention* or approach* or psychotherap* or training or treatment or technique* or program* or counseling or counselling)):ti,ab,kw
#9 ((behaviour* or behavior* or meditation) near (strateg* or intervention* or therap* or approach* or psychotherap* or technique* or counseling or counselling)):ti,ab,kw
#10 #4 or #5 or #6 or #7 or #8 or #9
#11 #3 and #10

CONTRIBUTIONS OF AUTHORS

TF, RC and JWSV conceived and all authors contributed to the design of the study. TF drafted and revised the protocol and all authors commented critically for intellectual content. DH contributed substantially to the revision of the protocol. All authors gave final approval of the document to be published.

Planned author contributions to the tasks for the full review are as follows:

- The Cochrane ENT Information Specialist will develop and run the search strategy.
- TF will obtain copies of the studies with the assistance of Maastricht University Library.
- TF, RC and DH will be responsible for the selection of studies.
- TF, RC and BM will be responsible for data extraction.
- TF, AW and DH will be responsible for assessing risk of bias.

- TF will enter the data into RevMan.
- TF, RC, DH and a statistician will conduct the analysis.
- All authors will contribute to the interpretation of the analysis.
- All authors will contribute to the drafting and updating of the review.

DECLARATIONS OF INTEREST

Thomas Fuller: none known.

Rilana Cima: was an investigator and author of the Cima 2012 study, which was a randomised controlled trial comparing stepped CBT-based care with treatment as usual for tinnitus reactivity and impairment.

Berthold Langguth: has received funding for research from the Deutsche Forschungsgemeinschaft, the German Ministry for Research, the American Tinnitus Association, the Tinnitus Research Initiative, the European Union, Otonomy and Sivantos. He has received consultancy and speaker honoraria from Autifony, ANM, Astra Zeneca, Kyorin, Merz, McKinsey, Microtransponder, Neuromod, Novartis, Pfizer, Lundbeck and Servier.

Birgit Mazurek: has received funding for research from the Deutsche Forschungsgemeinschaft, the German Ministry for Research, the American Tinnitus Association and the German Tinnitus Association Charité.

Angus Waddell: none known.

Derek J Hoare: is Chair of the British Society of Audiology tinnitus and hyperacusis special interest group.

Johan WS Vlaeyen: was an investigator and author of the Cima 2012 study, which was a randomised controlled trial comparing stepped CBT-based care with treatment as usual for tinnitus reactivity and impairment.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

Infrastructure funding for Cochrane ENT

- SWOL Limburgs Fonds voor Revalidatie and Netherlands Organisation for Health Research and Development (ZonMW), Netherlands.

Research programme: Health Care Efficiency, Subprogramme: Effects & Costs, Grant number: 945-07-715 provided funding for the employment of Thomas Fuller

NOTES

A previous Cochrane Review of 'Cognitive behavioural therapy for tinnitus', which is now out of date, will be withdrawn on the completion of this review (Martinez-Devesa 2010).