

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Evaluation and Treatment of Tinnitus: Comparative Effectiveness*

Draft review available for public comment from October 31, 2012 to December 4, 2012.

Research Review Citation: Pichora-Fuller MK, Santaguida P, Hammill A, Oremus M, Westerberg B, Ali U, Patterson C, Raina P. Evaluation and Treatment of Tinnitus: Comparative Effectiveness. Comparative Effectiveness Review No. 122. (Prepared by the McMaster University Evidence-based Practice Center under Contract No. 290-2007-10060-I.) AHRQ Publication No. 13-EHC110-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.



Commentator & Affiliation	Section	Comment	Response
Reviewer #1	a. General Comments:	<p>This is a comprehensive and well-executed systematic review that evaluates three key questions in relation to the management of idiopathic tinnitus: measures used to assess patients for subsequent management (KQ1), effectiveness of treatments (KQ2), and identification of prognostic factors (KQ3). Overall, the research questions are relevant, the methodology is clear, stringent and appropriate, and the review is well written. Thus, my general impression is favorable and I believe the review can provide appropriate recommendations for practice and further research based on the extent evidence. There are, however, some points that need to be addressed by the authors of the review.</p>	Thank you.
Reviewer #1	a. General Comments:	<p>A general comment I have is that some of the conclusions that were drawn are inconsistently presented throughout the manuscript.</p> <p>Most significantly, the abstract states that CBT interventions “does not affect perceived loudness”, but condensed review states that CBT interventions “showed improved perception of loudness relative to inactive comparators” (e.g., p. ES-12, lines 33-34).</p> <p>Check the main conclusions and the phrasing throughout the review, so that these are consistently reported in the same manner.</p>	<p>We have tried to address these concerns in the final version of the report.</p> <p>The SA gives a broad overview and overall the conclusion was that CBT did affect loudness but for specific CBT interventions there was some evidence of benefit. We have attempted to clarify this and standardize the phrasing throughout the report.</p>
Reviewer #1	a. General Comments:	<p>Whenever strength of evidence is reported (SOE), the overall conclusion that was reached based on that evidence should be provided in order to make it easy for the reader to interpret the finding. If only SOE is reported it might be misinterpreted.</p>	We have clarified the report to address the reviewer’s comment and SOE statements are accompanied by the overall conclusion.



Commentator & Affiliation	Section	Comment	Response
Reviewer #1	a. General Comments:	<p>In my opinion, the classifications of interventions are in certain cases not correct.</p> <p>Most significantly, Tinnitus Retraining Therapy (TRT) is classified into the category “Psychological/Behavioral Interventions” rather than “Sound Technologies”. This does not make sense, given that main component of TRT is to provide sound enrichment by sound generators and by using background sounds in the environment. Similar, specific studies are classified into “wrong” sub-categories (please see specific comments regarding the results).</p>	<p>We agree with the reviewer that TRT spans both the “Sound Technology” and “Psychological/Behavioral” Categories. We have added an explanation for our decision to put TRT in its own sub-category under the main category of Psychological/Behavioral treatments. “Since TRT depends on both the use of sound and counseling, it could be considered to span our two main categories of Psychological/Behavioral or Sound Technologies interventions; however, for the purposes of the present review, TRT is a unique sub-category and it has been situated in the Psychological/Behavioral category because the therapy specifically requires more than just the use of technology and TRT is most often compared to other treatments situated in the Psychological/Behavioral category rather than being compared to other technologies. Also note that other interventions categorized as Psychological/Behavioral do not preclude the use of technology; e.g., individuals with hearing loss would be expected to try hearing aids to address communication needs whether or not there is an intention for hearing aids to provide relief from tinnitus.”</p>

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Reviewer #1	a. General Comments:	<p>I also believe that clarity of presentation can be improved.</p> <p>The broad classifications should be used in the presentation of results and conclusion, and it should be clear whenever the authors are presenting a sub-category (e.g., CBT) within the head/main category (e.g., Psychological Interventions).</p> <p>Also, use the same reporting style for each category. For example, the text describing the conclusions in the abstract and in the summary/conclusions could be improved by having the same structure for all categories – for example, using the same outcomes for all reviewed categories, provide the main conclusions for all head categories in addition to sub-categories, provide both SOE and conclusion regarding effectiveness. Otherwise, the findings may be misinterpreted (e.g., that CBT does not have an effect on perceived loudness, but all other interventions do, because it is not explicitly stated in the abstract)</p>	<p>All results are presented within the four groupings of interventions (Pharmacological, Medical, Sound Technologies and Psychological and Behavioural Interventions). Within these broad groupings the results have been summarized with specific reference to subcategories.</p> <p>The abstract unfortunately, is limited to 250 words. We cannot provide the level of detail the reviewer has requested in this particular section of the report. The more detailed information is available in the Executive Summary and the full report which we have revised to improve clarity.</p> <p>We have attempted to make the report more easily cross-referenced. Thanks for the suggestions.</p>
Reviewer #1	a. General Comments:	Also, to enhance readability and transparency, I would prefer if the main conclusions could be summarized in bullet points at the end.	We have developed “summary boxes” containing key messages from the review findings.
Reviewer #1	b. Introduction:	The introduction provides a good background to the area and describes the rationale for the review in the context of what is already known.	Thank You.



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Reviewer #1	b. Introduction:	The only problem I have with the introduction is the descriptions/ definitions of interventions. First, TRT should be presented as a subcategory in the main category “Sound Technologies”. In addition, in the paragraph describing TRT (p. 5, lines 55-56), it is stated that TRT involves fairly extensive counseling. Revise this sentence and clarify how much time is devoted to directive counseling/education and sound generators, according to the TRT protocol.	We agree with the reviewer that TRT spans both the “Sound Technology” and “Psychological/Behavioral” Categories. We have added an explanation for our decision to put TRT in its own sub-category under the main category of Psychological/Behavioral treatments. “Since TRT depends on both the use of sound and counseling, it could be considered to span our two main categories of Psychological/Behavioral or Sound Technologies interventions; however, for the purposes of the present review, TRT is a unique sub-category and it has been situated in the Psychological/Behavioral category because the therapy specifically requires more than just the use of technology and TRT is most often compared to other treatments situated in the Psychological/Behavioral category rather than being compared to other technologies. Also note that other interventions categorized as Psychological/Behavioral do not preclude the use of technology; e.g., individuals with hearing loss would be expected to try hearing aids to address communication needs whether or not there is an intention for hearing aids to provide relief from tinnitus.”
Reviewer #1	b. Introduction:	Similar, the definition of CBT for tinnitus and the rationale for using such interventions is not clear. Revise the section. Although CBT is somewhat difficult to define, it is important to acknowledge that CBT is not one form of treatment-protocol, but can consist of several different procedures, including cognitive techniques, behavioral techniques and any combination of cognitive/behavioral techniques (e.g., Andersson, 2002; Henry & Wilson, 2001). It is also important to acknowledge that these interventions should be presented within a psychological theoretical CBT-consistent framework (e.g., learning and or/cognitive theories of affect regulation and behavior change, e.g., Hesser et al., 2011). Furthermore, the main idea of CBT-based interventions is not to target associated depression/anxiety, as described here – although no mutually exclusive – but to change psychological processes thought to maintain/exacerbate distress associated with tinnitus.	The material about depression and anxiety has been moved under the general psychological/behavioral heading and no longer appears under the CBT heading. The reviewer’s suggestions for describing CBT have been added to the material explaining CBT.

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Reviewer #1	c. Methods:	The methodology used is appropriate and is for most part clear. Eligibility criteria, search strategies, study selection, risk of bias are appropriate described. Some minor clarifications are, however, needed.	Thank You.
Reviewer #1	c. Methods:	In the Quantitative Synthesis section, it is stated that the authors used a correlation between pre- and post-treatment of 0.69 in the calculation of effect sizes (p. 19, line 35-36). Although the authors cited previous research here, it is unclear to me why this estimate was chosen. Please clarify this.	The authors of the Cochrane review and previously published systematic reviews, used this estimate. This reference has been added to the review. The Cochrane review utilized individual patient data (IPD) from several studies to compute the correlation between pre and post scores. They then used this estimate to assist in the computation of all of their meta-analyses. It should be noted that we also carried out sensitivity analyses using different potential correlations, and the results were unchanged as is mentioned in methods section.
Reviewer #1	c. Methods:	Please also clarify who conducted the ratings of strength of evidence and who extracted the data from the studies. In addition, can any evidence be put forward to that ratings and data extraction procedures were reliable (e.g., inter-rater reliability).	The judgments for the strength of evidence were determined by two of the study authors. The combination of authors varied with the section. The raters were experienced in undertaking systematic reviews or in audiology.
Reviewer #1	c. Methods:	Please also add a section about the control conditions used in the studies and how they were categorized, that is, active, inactive, placebo, etc.	The following definitions were provided in Table 2: Inactive controls (including placebo; no treatment; wait list; sham interventions) Active controls (including treatment as usual; other intervention/treatments)
Reviewer #1	d. Results:	The result section is presented in a transparent and clear manner and includes the most relevant results (e.g., included studies, selection process, results of individual studies and synthesis of the results for each treatment modality).	Thank You.



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Reviewer #1	d. Results:	First, as mentioned in the general comments, TRT is wrongly included in the psychological main treatment category.	We agree with the reviewer that TRT spans both the “Sound Technology” and “Psychological/Behavioral” Categories. We have added an explanation for our decision to put TRT in its own sub-category under the main category of Psychological/Behavioral treatments. “Since TRT depends on both the use of sound and counseling, it could be considered to span our two main categories of Psychological/Behavioral or Sound Technologies interventions; however, for the purposes of the present review, TRT is a unique sub-category and it has been situated in the Psychological/Behavioral category because the therapy specifically requires more than just the use of technology and TRT is most often compared to other treatments situated in the Psychological/Behavioral category rather than being compared to other technologies. Also note that other interventions categorized as Psychological/Behavioral do not preclude the use of technology; e.g., individuals with hearing loss would be expected to try hearing aids to address communication needs whether or not there is an intention for hearing aids to provide relief from tinnitus.”
Reviewer #1	d. Results:	Furthermore, the Cima et al. (2012) trial has been classified as TRT (with the addition of CBT-interventions), despite the fact that the study authors themselves name the treatment that was tested as a special form of CBT treatment. It is unclear to me why the authors of the review classified it as TRT, as the main components of the treatment-protocol used in the Cima trial are not TRT-based.	The treatment in question is a hybrid of CBT and TRT. The authors describe their novel intervention as: “specialised care of cognitive behaviour therapy with sound-focused tinnitus retraining therapy or usual care” In this review, we felt that the intervention fit in with the other TRT reports. We do not believe that the results would be altered if it had been grouped with the CBT studies.

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Reviewer #1	d. Results:	Classifying the Kaldo et al. (2007) trial and the Westin Zetterqvist et al. (2011) trial as not CBT-based is not correct. The Kaldo trial used a different delivery format, but the protocol was based on CBT-procedures and employed a modified version of the protocol that was used in the Andersson et al. (2002, 2005) studies, which were classified as CBT in the current review. Similar, Acceptance and Commitment Therapy (ACT) is a modern form of CBT, which is rooted within the behavioral tradition of CBT, and the founders of ACT have always said that the treatment is part of the CBT-tradition (see for a recent discussion about this by one of the founders, e.g., Hayes et al., 2011). Given that no sub-analyses were conducted on different delivery formats or different forms of CBT, these studies should be included in the CBT-category.	We understand that there is some similarity between CBT and the self-help and telephone therapy of Kaldo 2007 study and the Acceptance and Commitment Therapy of the Westin 2011 study. We also agree that we could have chosen to place these studies in the CBT sub-category. Initially, we were guided by the author's choice in labeling the intervention. We believe there is a fine line in making these categorization decisions and, changing the sub-category of the study would not alter the overall conclusions of our review. The 'tricky' nature of these decisions was commented on by another reviewer who concurred that changing the sub-categories would not alter the conclusions. Nevertheless, we have followed your suggestion and move the Kaldo and Westin papers from the other sub-category to the CBT category.
Reviewer #1	d. Results:	The review has also missed to include two recent RCTs evaluating the efficacy of different forms of CBT-based interventions, both reports published as advanced online publications before June 2012: Philippot, P., Nef, F., Clauw, L., Romrée, M., & Segal, Z. (2011). A randomized controlled trial of mindfulness-based cognitive therapy for treating tinnitus. <i>Clinical Psychology & Psychotherapy</i> , 19(5), 411-419. Hesser, H., Gustafsson, T., Lundén, C., Fattahi, K., Henrikson, O., Johnsson, E., Zetterqvist Westin, V., Mäki-Torkko, E., Carlbring, P., Kaldo, V., & Andersson, G. (2012). A randomized controlled trial of Internet-delivered cognitive behavior therapy and acceptance and commitment therapy in the treatment of tinnitus. <i>Journal of Consulting and Clinical Psychology</i> , 80, 649 -661.	These studies were not captured in our search last updated June 2012 as they had not yet been indexed in the databases we searched. We note these studies in the discussion.



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Reviewer #1	e. Discussion/ Conclusion:	<p>The results are, with a few exceptions, appropriately discussed in the context of limitations at the level of the individual study and of the syntheses of results. I particularly found section “Further Research Recommendations” as valuable, concise and informative.</p> <p>It is also noteworthy that TRT is discussed in the sound technology section rather than psychological section, which, in my opinion, is more correct (see my previous comments).</p>	<p>Thank You.</p> <p>We agree with the reviewer that TRT spans both the “Sound Technology” and “Psychological/Behavioral” Categories. We have added an explanation for our decision to put TRT in its own sub-category under the main category of Psychological/Behavioral treatments. “Since TRT depends on both the use of sound and counseling, it could be considered to span our two main categories of Psychological/Behavioral or Sound Technologies interventions; however, for the purposes of the present review, TRT is a unique sub-category and it has been situated in the Psychological/Behavioral category because the therapy specifically requires more than just the use of technology and TRT is most often compared to other treatments situated in the Psychological/Behavioral category rather than being compared to other technologies. Also note that other interventions categorized as Psychological/Behavioral do not preclude the use of technology; e.g., individuals with hearing loss would be expected to try hearing aids to address communication needs whether or not there is an intention for hearing aids to provide relief from tinnitus.”</p>

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Reviewer #1	e. Discussion/ Conclusion:	<p>Three independent systematic reviews and meta-analyses (Hesser et al., 2011; Hoare et al., 2011; Martinez-Devesa et al., 2010) have concluded that CBT-based interventions have an effect on tinnitus-specific quality of life measures as compared with active controls.</p> <p>This review also concludes that these interventions have an effect on the outcome, but only compared with inactive controls. This might be a result of differences with regard to classification of studies (as mentioned in previous comments), selection of studies, interpretation of results, or to different definitions of active vs. passive control conditions. Nevertheless, this discrepancy in conclusion should be appropriately acknowledged and discussed.</p>	<p>These reviews are noted in the discussion. We do not think that there is a discrepancy in our conclusions and the conclusions of other reviews that there seems to be benefit from CBT-based interventions for tinnitus-specific quality of life.</p> <p>Our systematic review included studies with active and inactive controls. We presented the findings of the inactive controls in the forest plots and the strength of evidence ratings. We did not undertake subgroup analyses to compare those studies with active relative to inactive controls. We have added text to the discussion to address issues concerning active vs. inactive controls.</p>
Reviewer #1	e. Discussion/ Conclusion:	I believe that an important target for further research (basic research) is also to address specific hypothesis of how distress is maintained or exacerbated among individuals with tinnitus, as this may improve the development of key interventions that can explicitly target proposed processes of symptom exacerbation. This also involves improvement of theoretical models of tinnitus severity.	<p>We have added the following future research recommendation for KQ2 “other” category</p> <p>“To develop or improve theoretical models about tinnitus severity and how distress is maintained or exacerbated in these patients.”</p>
Reviewer #1	e. Discussion/ Conclusion:	In addition, I would recommend the authors to also include bullet points for the main conclusions/summary.	Thank you, bullets have been added.
Reviewer #1	f. Clarity and Usability	I believe the authors can improve the utility of the review by providing clear practical recommendation at the end of the summary (see also the last result comment). Please see my general comments with regard to clarity.	Thank you, bullets have been added to clarify.
Reviewer #2	General Comments: Structured Abstract (p. 6) Objectives:	Suggested edit: “A review was undertaken to evaluate the peer-reviewed literature with respect to three elements of tinnitus management: (1) measures used to assess patients for management needs (Key Question 1); (2) effectiveness of treatments (Key Question 2); and (3) identification of prognostic factors (Key Question 3).”	Thank you. We have modified the structured abstract as suggested.
Reviewer #2	General Comments: Structured Abstract (p. 6) Conclusions:	(1) Do not include the use of sound as effective for tinnitus management. Clearly, sound can be effective, but we don’t know what type of sound or sound delivery is most effective. The Cochrane Review article concluded that sound therapy is effective when delivered in conjunction with counseling.	The conclusions in the abstract do not mention sound-based interventions.

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Reviewer #2	General Comments: Structured Abstract (p. 6) Conclusions:	(2) There is no evidence that pharmacological interventions have any effect on the loudness or other psychoacoustic attributes of tinnitus.	The strength of evidence for subjective loudness, which we evaluated in this report, is low or insufficient. The structured abstract conclusions have been modified to reflect these findings.
Reviewer #2	General Comments: Structured Abstract (p. 6) Conclusions:	(3) There is evidence that pharmacological interventions can improve mental health conditions (anxiety, depression, PTSD) and insomnia that are comorbid with tinnitus.	SOE for sleep disturbance, anxiety, and depression is insufficient, The structured abstract conclusions have been modified to reflect these findings.
Reviewer #2	p. 11:	The distinction between “objective” and “subjective” tinnitus is outdated. In general, there are two ways of making a dichotomous distinction: (1) There is tinnitus that is generated acoustically within the head or neck. This is real sound and is referred to as “somasounds” or “somatic tinnitus.” Some refer to this type of tinnitus as “objective” tinnitus. Tinnitus can also be modulated by somatic manipulations (touching areas of the head/neck; moving the eyes, etc.). Some refer to this type of tinnitus as “objective” tinnitus. I prefer to refer to it as “somatically modulated” tinnitus. (2) There is tinnitus that is generated neurophysiologically within the auditory pathways. This can be referred to as “neurophysiologic” tinnitus, “subjective” tinnitus, or just “tinnitus.”	We have added the suggested alternative terms that might be used to refer to objective tinnitus. As explained in the text, our decision to use the term “subjective idiopathic tinnitus” was because it was the most commonly used term. We are not claiming that it is the latest or most accurate term. Other reviewers have commented that the term we used was a good choice for the present purposes.
Reviewer #2	p. 11:	“Idiopathic” tinnitus is also outdated. Although this term has a specific meaning, it is not necessary because all “neurophysiologic” or “subjective” tinnitus is idiopathic, i.e., we do not know the neural mechanisms that trigger and sustain tinnitus.	We have added the suggested alternative terms that might be used to refer to objective tinnitus. As explained in the text, our decision to use the term “subjective idiopathic tinnitus” was because it was the most commonly used term. We are not claiming that it is the latest or most accurate term. Other reviewers have commented that the term we used was a good choice for the present purposes.

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Reviewer #2	p.11	<p>The list of possible interventions for tinnitus lumps well-researched and documented methods of tinnitus management along with numerous “complementary and alternative” methods. I think these should always be distinguished. Some methods have credibility and most do not, so it is misleading to just provide a single list that includes both. Also, Neuromonics is the only method of tinnitus management that refers to a company.</p> <p>This method should be mentioned separately because it is a for-profit company and not just a “method” that anyone can use (any implementation of Neuromonics requires company training and support). Also, all articles written about Neuromonics are written by people who are somehow affiliated with the company. The quote on the next page is inappropriate because this is quoting from the company’s promo material—it is not an objective statement from an impartial researcher.</p>	<p>We agree with the reviewer about the remarkable heterogeneity of the treatments that have been proposed for tinnitus. Our mandate was to consider all possible treatments and to evaluate their comparative effectiveness. Comments about the wide range of possible interventions have been added to the introduction. Comments about commercial interest have been added elsewhere. Quotes and references to non-scientific sources such as websites of companies or consumer associations are transparent insofar as the sources are cited. We believe that the results of our review do reflect the merits of the various interventions in a fair fashion based on the evidence we found, including an assessment of the strength of the evidence and the risk of bias as well as consideration of other limitations.</p>
Reviewer #2	p. 19, 2nd para, 2nd line:	What does “the study protocol” refer to?	<p>The study protocol means the protocol outlining the methodology for the systematic review designed to address these research questions for the systematic review. In accordance with AHRQ policy, this protocol was developed with input from clinical experts</p>
Reviewer #2	pp. 19, 27, 43 “Medical Interventions”	<p>the listed types of studies I would not consider medical interventions. I would consider medical interventions to include prescription medications and surgeries. The types of studies listed (rTMS, LLLT, acupuncture, and ARCNI) would be considered complementary and alternative methods.</p>	<p>It is always problematic to provide a label for a group of disparate interventions. Initially, these interventions were grouped together and labeled ‘medical’ because drugs and surgeries are commonly considered to be medical treatments. Some of the less common treatments that are not typically administered or that exceed the scope of practice of audiologists were also included in this general ‘medical’ section. . According to National Centre for Complementary and Alternative Medicine a division of the National Institute of Health in the United States of the treatments listed only acupuncture is a CAM therapy</p>
Reviewer #2	Intro, Methods, Results, Disc, Conc, Clarity&Usability	willing to comment more in the future	Thank You.

Commentator & Affiliation	Section	Comment	Response
Reviewer #3	a. General Comments	The report is clinically meaningful. the general comments are appropriate.	Thank You
Reviewer #3	b. Introduction	Tinnitus is discussed appropriately in general. I am not confident about some claims (tinniuts is caused by cerumen...etc) but these are in the literature so the authors can't be faulted much.	Thank You
Reviewer #3	c. Methods	The report is clinically meaningful. The target populaitons and questions are fairly well defined.	Thank You
Reviewer #3	Population Inclusion criteria	<p>KQ1: Adult (≥ 18 yrs) patients who visit healthcare practitioners with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds, etc.):</p> <p>This is unclear. Was the criterion patients who visited practitioners BECAUSE of tinnitus or were all patients who presented for all reasons interviewed and were asked if they had tinnitus. The difference is important in controlling bias toward patients who were upset about tinnitus as opposed to those who accept tinnitus. Of course the authors found no acceptable studies for this question anyway.</p>	The criterion would have allowed studies with participants selected from those who visited practitioners and reported tinnitus, whether or not tinnitus was the main reason for the visit. In any case, as the reviewer recognizes, we did not find any studies that compared the effectiveness of different methods of assessment to determine whether further evaluation or treatment of tinnitus was needed.
Reviewer #3	KQs 2 & 3	<p>Adults (≥ 18 yrs) with a diagnosis of subjective idiopathic (nonpulsatile) tinnitus who are sufficiently bothered by tinnitus that they are seeking a treatment intervention. It is not clear if this criterion is different from KQ1 Interventions inclusion criteria:</p> <p>KQ1: Direct observation or observation of sound with stethoscope; referral to a health professional with expertise on managing tinnitus (i.e., otolaryngologist, audiologist, neurologist, mental health professional); administration of scales/questionnaires to assess severity (e.g., THI, TRQ, TFI, VAS, etc.).</p> <p>Notably absent is the assessment of hearing. Standard evaluation or tinnitus includes assessment of hearing. Hearing status is an important factor in tinnitus. It appears that the authors feel that auscultation with a stethoscope is more important than audiometry.</p>	<p>The criteria for KQ1 differ from those for KQ2 and KQ3. The focus of KQ1 was on the effectiveness of methods for determining whether or not patients needed further evaluation or treatment for tinnitus, whereas KQ2 and KQ3 focused on the comparative effectiveness of treatments, assuming that only those who needed treatment would be studied.</p> <p>The intention of KQ1 was to include studies that might have investigated the methods used by any type of practitioner, including primary care physicians. A primary care physician might use a stethoscope or give a questionnaire but would most likely refer to another professional for hearing assessment rather than conducting audiometry. Of course, if a study had investigated the methods used by health professionals with expertise on managing tinnitus, then a broader range of test methods might have been evaluated. Had we found such studies then they would have been included</p>

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Reviewer #3	Data extraction	<p>References for the Newcastle-Ottawa quality assessment scales for case-control studies and cohort studies,15 and the Jadad scale for RCTs16.</p> <p>I don't see these cited in the references (page 271). I did an online search. They look like reasonable attempts to standardize data extraction, but the authors should be aware that these are new tools with less acceptance than the methods that they are criticizing. They also have biases the exclusions that should be discussed. For example the Jadad scale places great emphasis on blinding, which can be problematic in tinnitus research.</p> <p>Nevertheless, introduction of bias by adopting particular, strict theoretical framework is a common problem in serious reviews.</p>	<p>The NOS and Jadad scale citations are included in the reference list.</p> <p>Wells, G. A., Shea, B., O'Connell, D. et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. www.ohri.ca/programs/clinical_epidemiology/oxford.aspAccessed:4-11-2013.</p> <p>Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17(1):1-12. PM:8721797</p> <p>We agree with the peer reviewer that no scale attempting to address risk of bias is perfect. However, both of these scales are considered to be reliable and valid and are widely used.</p> <p>Blinding is a problem in many types of intervention studies, and is not unique to tinnitus research. As such, even if it is difficult it still poses a risk of bias. The purpose of the tools is to determine this degree of bias. If all studies fail for a particular criteria (for example blinding) then this will not really help us distinguish amongst the studies per se, but they are still at risk of bias.</p>
Reviewer #3	RESULTS	<p>I find the grouping of results confusing. The authors report psychological interventions that include various antidepressants, and then include depression as a different factor with anxiety.</p> <p>“Sleep disturbances were treated with antidepressants and other medications.</p> <p>Later they report “medical” interventions but do not realize that antidepressants and depression are related or that drugs can be a medical intervention.</p> <p>Given the tremendous overlap and unwillingness to separate the entities it is difficult to determine whether one was helpful compared to the others or not.</p>	<p>We recognize the existence of areas of overlap and agree that no ideal means exists to group the interventions into distinct categories. Our final groupings were based on our clinical knowledge and input from the Technical Expert Panel. We made small modifications or clarifications to the groupings, where necessary, based on earlier feedback (see our responses to other comments).</p>



Commentator & Affiliation	Section	Comment	Response
Reviewer #3		<p>There is a lack of understanding about the various medical problems.</p> <p>The definitions of depression, anxiety, sleep disorders and most subjective features received much less consideration than the statistics. There are well-developed tools for these, but generally these were not applied in the literature.</p> <p>This was ignored in the review probably because such considerations would preclude the review being done at all.</p> <p>Particularly concerning is the definition cognitive behavioral therapy (CBT) because that is the one intervention that the authors found some evidence to support. The definition of CBT varies widely and there are different forms of this therapy in different centers.</p>	<p>We agree that the topic is complicated by co-morbidities and that it is difficult to parse out the contributions (or not) of various medical conditions and we tried to make this point in several places in the review.</p> <p>We agree that many of the outcome measurement instruments used in the included studies had problems. We discussed these issues throughout the report and provided recommendations for future research.</p> <p>We have revised the explanation of CBT, including unifying principles as well as comments about variations in practice.</p> <p>We agree that the definition of CBT varies and we have indicated in the introduction that CBT encompasses a number of possible therapeutic procedures. Throughout the report, we describe the different variants of CBT.</p>



Commentator & Affiliation	Section	Comment	Response
Reviewer #3		Assessing Tinnitus-specific quality of life as opposed to global quality of life is a good idea, but it is very difficult to be sure that any complaint is specific to that symptom or represents somatization and generalization. For example, subject who blame tinnitus for various problems may really be depressed or anxious or something else. How do we validate that quality of life is really tinnitus-specific?	<p>These instruments are “tinnitus specific” because the original development of these instruments was specific for tinnitus patients and validated in tinnitus patients. In contrast, the instruments included as outcomes for depression and anxiety were developed to assess those problems in a general population without regard to tinnitus. Similarly, the instruments included as outcomes for global quality of life were developed for use in a general population without regard to tinnitus.</p> <p>There may be overlap in areas covered within the Tinnitus specific quality of life instruments and other domains. For example, there may be some questions about mood in the Tinnitus Handicap Instrument. However, this does not mean that the person has clinical depression. The degree of depression would have to be established using depression specific instruments. For this reason, the primary purpose for which the instruments were developed informed our decision to use them as measures of the outcome categories for the purpose of the present review.</p>
Reviewer #3	d. Results	The results are pretty clear generally considering the vague nature of the subject matter. The authors report determination of bias and I am not certain how that was assessed actually, and whether this method was reproducible or not. It appears that this assessment was a guess by more than one of the reviewers. This approach introduces bias.	The methods section (chapter 2) specifies how risk of bias was evaluated. The raters judging risk of bias had graduate training in epidemiology and were able to assess the eligible studies. Two raters examined each study independently using standardized assessment forms, which are included in the Appendices of the report.
Reviewer #3		I liked the reference to the finding that ground up honeybee larvae were effective treatment. It is humorous and entertaining, but still is a recommended treatment in the literature so it deserves to be in there. I don't think I will be raiding any bee hives soon though.	We agree, thank you.
Reviewer #3	e. Discussion/ Conclusion	The results are pretty clear although I have some questions about the CBT findings as discussed above. The directions for research are clear, but obvious and banal.	Thank You.

Commentator & Affiliation	Section	Comment	Response
Reviewer #3		Although my review might appear to be negative, it is obvious that the authors have put a lot of work into this assessment and have done well in trying diligently to attack a problem that is vague and difficult.	Thank You.
Reviewer #3	f. Clarity and Usability	<p>The organization is good given the nature of the topic. The authors have put a lot of work into this and have tried hard to provide a balanced review.</p> <p>Basically this is a negative review of treatment of tinnitus, which is already the established notion in the literature. Inasmuch as no new treatment recommendations were identified there will be minimal clinical impact.</p>	Thank You.
Reviewer #4	a. General Comments	The report addresses a clinically meaningful problem, chronic tinnitus. The symptom affects a small percentage of the population, but can have a significant negative effect on quality of life. A thorough and well-performed critical evaluation of the existing literature on tinnitus management strategies would be an important contribution.	Thank You.
Reviewer #4	a. General Comments	<p>The target populations are explicitly defined.</p> <p>The report is not sufficient to guide either medical decision making, health care policy or reimbursement and coverage policies.</p> <p>The report is useful in explicitly stating the limitations of the current literature.</p>	The McMaster EPC was charged with reviewing a body of evidence to address three specific key questions. Our final report is a reflection of the current state of the evidence relating to these questions. We agree with the reviewer that the current evidence is insufficient to guide medical decision making, healthcare policy, or reimbursement decisions. The purpose of an evidence report is to present evidence. The McMaster University Evidence-based Centre is not tasked with making policy recommendations.
Reviewer #4	a. General Comments	<p>The first key question is difficult to understand and the utility of the question is questionable.</p> <p>It seems that the question is asking if there are data evaluating tinnitus assessment tools that stratify patients into 'need to treat'/'no need to treat' categories. The clinical reality is that all patients are seen in clinic because they are seeking treatment of some type. The treatment may be as simple as evaluation, reassurance and education or more complex (medications, acoustic enrichment, etc.).</p>	The reviewer is correct about what the question is asking; however, our intention was to ask if there was evidence that a particular evaluation method was better than another at determining which patients needed further assessment or treatment after the initial consultation. The question was intended to be relevant to a wide range of practitioners including primary care physicians who need to decide whether or not to refer patients to specialists.

Commentator & Affiliation	Section	Comment	Response
Reviewer #4	a. General Comments	The second and third key questions are explicitly stated and appropriate. KQ#3 could not be answered using the authors search strategy criteria. This is surprising and may overlook significant contributions in the literature that are noteworthy.	The search strategy for KQ 3 was reviewed and approved by the TEP and our local team of tinnitus experts. The search criteria given in the PICOTS for KQ3 are very broad so we do not believe that eligible studies were excluded. We also examined publications that peer and public reviewers suggest we may have not captured in our comprehensive search Like the reviewer, we were surprised that no studies addressed KQ3 and the discussion underlines the need for future research to address this question.
Reviewer #4	b. Introduction	The statement that tinnitus increases with age (Line 15 Tinnitus increases with age ref 2) is not accurate. See Tinnitus: Theory and Management, Snow (ed.), Chapter 3, 2004.	We have provided references to support the statement that tinnitus (and hearing loss) increase with age. Davis A, Smith P, Ferguson M, et al. Acceptability, benefit and costs of early screening for hearing disability: A study of potential screening tests and models. Health Technol Assess. 2007;11(42):iii-xii, 1-154. PMID:17927921 We have also added a new reference regarding differences in reports of tinnitus depending on birth cohort: Nondahl DM, Cruickshanks KJ, Huang GH, et al. Generational differences in the reporting of tinnitus. Ear Hear. 2012;33(5):640-4. PM:22588269 Since more recent cohorts report tinnitus more that earlier cohorts when age is controlled, this may mask longitudinal age-related increases in tinnitus.
Reviewer #4	b. Introduction	The inclusion criterion 'observation with a stethoscope' in table ES-1 for KQ1 would seem to be in error, if subjective tinnitus is being evaluated.	The evaluation methods included for KQ1 were all those that might be used by a practitioner in order to determine if a patient needed further assessment or referral by a specialist. Observation with a stethoscope could be used in such an initial evaluation. Although KQ2 and KQ3 are limited to patients with subjective idiopathic tinnitus, KQ1 is not.
Reviewer #4	b. Introduction	The statement that patient education about tinnitus is 'no treatment' (p.43) is in error. There is high therapeutic value in educating patients about their symptoms.	This statement has been reworded to clarify that no recommendation for treatment may be made at the initial assessment although information may be provided at that time.

Commentator & Affiliation	Section	Comment	Response
Reviewer #4	b. Introduction	The statement that tinnitus is largely viewed as a psychological problem (p.2) is misleading and arguably does not reflect the opinions of many people who work in the field.	Our intention was to note the SHIFT from earlier thinking about tinnitus as being only an auditory problem to more recent thinking of it as a problem of psychological significance. This trend is consistent with general approaches to chronic disabilities shifting from a biophysical perspective to a more biopsychosocial perspective that recognizes that people can learn to cope with problems when cures are not available. References in support of this observed shift are provided and the wording has been modified.
Reviewer #4	b. Introduction	Hearing aids provide benefit beyond decreasing level of awareness of tinnitus (p.44).	We agree with the reviewer. The text says that hearing aids are one option for helping to reduce reactions to tinnitus and then we go on to say that it is possible to achieve the goals of sound therapy with hearing aids.
Reviewer #4	c. Methods	<p>The inclusion/exclusion criteria for KQ2 are incomplete.</p> <p>Why are 'within-subject controls' not included as comparators?</p> <p>Why isn't objective loudness measured in decibels included in Outcomes of Benefit?</p> <p>Why is measurement in decibels an exclusion criterion?</p>	<p>We included studies in which post-treatment scores are compared to pre-treatment scores. We needed to have studies that compared a treatment to a control group or to another treatment group.</p> <p>The decision to exclude loudness measured in dB as an outcome was made in consultation with our technical experts and key informants. Subjective measures of loudness were retained as eligible outcome measures because they were felt to best represent an individual's experience of tinnitus. Decibels are a unit of sound intensity or pressure which is a physical acoustical dimension and dB is not a unit that is meaningful for the measurement of psychological dimensions. This distinction is similar to the distinction between Hz as a physical dimension and pitch as a psychological dimension.</p>



Commentator & Affiliation	Section	Comment	Response
Reviewer #4	c. Methods	<p>The search strategies are explicitly stated. I do not believe that the strategies resulted in the most appropriate and unbiased view of the clinical problem.</p> <p>For example, querying an advocacy organization (the American Tinnitus Association) likely leads to a very biased view of the problem.</p> <p>The American Academy of Otolaryngology Head and Neck Surgery, the national organization of Otolaryngologists, was not queried.</p>	<p>We searched the websites of these organizations for any additional studies that might not have been indexed within traditional bibliographic sources. Any grey literature found on these sites must then meet our eligibility criteria. We do not believe that this introduced bias.</p> <p>We did not contact members of these organizations to solicit their opinions. We did have ENT physicians in the TEP and acting as key informants, as well as someone from the American Academy of Otolaryngology</p>
Reviewer #4	c. Methods	The statistical methods are appropriate.	Thank You.



Commentator & Affiliation	Section	Comment	Response
Reviewer #4	d. Results	<p>The level of detail in the results section is appropriate. The study characteristics are clearly described.</p> <p>There is significant oversight of studies that should have been included in the review. The reasons for exclusion (comparators do not meet criteria, insufficient detail for data aggregation) may require re-assessment.</p> <p>Exclusion of well-designed and executed studies that significantly contribute to the literature, such as Bauer, Dineen, Dobie, Drew, Henry and Witsell, significantly detracts from the review.</p> <p>In contrast, inclusion and detailed discussion of poorly designed and reported studies, such as Tass 2012, is very misleading.</p> <p>Most significantly, the Tass study does not include a true control group (G5 subjects did receive some sound therapy), and there were only 5 subjects in the 'control' group. There was no control for hearing loss, and details on tinnitus pitch matching to select sound treatment are lacking.</p> <p>This study is categorized as a medical treatment, when in fact it is acoustic therapy.</p>	<p>Eligibility of studies was not based on the methodological quality of studies. Many of the included studies have important methodological flaws. The studies that were excluded did not meet at least one criterion of the eligibility criteria.</p> <p>We respectfully disagree with the reviewer, suggesting that we excluded well designed studies. We screened all studies and those that did not meet our criteria were excluded.</p> <p>There are many other studies currently included in the review that had about 5 subjects in the control group (please see the sound generator section and the psychological/ behavioral section) . The control group (G5) was included as a placebo group with the sound therapy they received selected so that it would not have the critical acoustic characteristics of the sort entailed in the treatment stimuli.</p> <p>We decided to put this treatment in its own sub-category in the medical section rather than with more traditional sound treatments because the acoustic sound applied in the Tass study requires the optimization of the stimuli based on EEG results. Typically, audiologists manage the selection of other sound technologies based on auditory assessments of tinnitus but they would not be qualified to administer the EEG required to select the stimuli for this particular treatment. For this reason it was grouped under medical. In addition, the authors propose this treatment as an alternative to versions of TMS therapy so it seemed advantageous to keep these two types of treatment in the same over-arching section.</p>
Reviewer #4		<p>There is conflicting information on which studies are included and excluded. For example, Dineen 1997 and 1999 is listed in the Excluded Studies (p.187) and is listed in Appendix D Table C "Characteristics of Included Studies".</p>	<p>Dineen 1997 & 1999 are included in Sound Technologies (Table 21 & AppD, Table C) They have been removed from the excluded studies list. Thank you for catching this.</p>

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Commentator & Affiliation	Section	Comment	Response
Reviewer #4	e. Discussion/ Conclusion	<p>The findings are clearly stated.</p> <p>The limitations of the studies are described adequately.</p> <p>There appears to be a fundamental flaw in the approach to study selection meeting criteria for review. This results in several significant studies not included in the review because of “insufficient detail for aggregation of data”, and the inclusion of studies that have much less face-value as unbiased evidence worthy of consideration.</p>	<p>Thank You.</p> <p>Eligibility of studies was not based on the quality of studies. Many of the included studies have important methodological flaws. The excluded studies did not meet our eligibility criteria because they did not provide data in a manner that allowed the calculation of SMD. See Appendix F and the expanded discussion.</p>
Reviewer #4		<p>The future research section is thorough, well-reasoned and will serve as an excellent guide. Many important points are made which will improve the quality of future tinnitus research. This, to my mind, is the most significant feature of this review.</p> <p>The authors make the distinction between statistically significant and clinically significant results. This is very important.</p>	Thank You.
Reviewer #4	f. Clarity and Usability	This is a highly detailed examination of the existing literature on tinnitus evaluation and treatment. It covers a large, diverse body of literature and compiles the data in a logical manner. There is some redundancy bordering on excessive detail. There is value in this for people currently or considering conducting tinnitus research. The details will not be of much utility for the general practitioner interested in the bottom-line on tinnitus treatments.	Thank You. We have prepared summary boxes that may assist clinicians and other readers. Clinician and summary patient guides will also be created in this report. In the report itself, we attempted to reduce areas of redundancy.
Reviewer #5	a. General Comments	The report is meaningful - if rather depressing reading. The key questions are likewise appropriate. I am not sure who the audience is.	The audience is all relevant stakeholders (patients, clinicians, and policy makers)
Reviewer #5	b. Introduction	<p>The introduction is largely straight forward. I have made a few points which are in the attached file.</p> <p>Firstly, congratulations on delivering a review of such a huge range of disparate research projects. I have gone through the review to the best of my abilities in the relatively short time available but do not claim to have exhaustively read and analysed every sentence – particularly not the main results section. I would like to make the following points:</p>	Thank You.
Reviewer #5	Page 5 Line 28	tapedectomy should read stapedectomy	We have corrected the spelling.



Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Page 11 Line 44	“treatment for temporomandibular joint (TMJ)disease as tinnitus is a key symptom in this problem”. This is a contentious area and there is alternative research suggesting that the association is just coincidence. I would therefore suggest toning this down a bit. Perhaps something like “treatment for temporomandibular joint (TMJ)disorder as tinnitus has been reported in association with this problem”	We have re-worded the text as suggested.
Reviewer #5	Page 11 Line 48	I would not regard hyperbaric oxygen as CAM! And I think the patient with gangrene or the diver with decompression sickness would agree that it is mainstream treatment not alternative.	We have modified this by making hyperbaric oxygen its own category within the grouping of medical interventions
Reviewer #5	Page 11 Line 49	Masking is a separate treatment from the more usual low level broad band sound therapy that is used in tinnitus management. Very few people try and mask nowadays. This is better dealt with in the main text rather than this executive summary section.	The text has been modified to separate maskers and sound generators as two items under sound-based treatments. The historical background is provided in the introduction of the main text.
Reviewer #5	Page 17 Line 31	Use of the word psychoactive. As I understand the word (and as it appears in medical dictionaries) a psychoactive drug is a compound that crosses the blood-brain barrier and has an effect on mood, behaviour, cognition etc. The definition used here of a “neurotransmitter drug” would include all manner of drugs including beta blockers for hypertension! Also, are antidepressants not psychoactive? And clonazepam? And Deanxit? It is also contentious as to whether gabapentin and baclofen have therapeutic psychoactive effects (they certainly have very well documented psychoactive side effects!). I cannot see any advantage to lumping these drugs together but if you do want to group them, the only thing they have in common is their mode of action which is stimulating or enhancing GABA (though the latest research suggests that is not how gabapentin works.....).	We removed the word ‘psychoactive’ from the report. We refer to gabapentin, baclofen, alprazolam, and acamprosate as neurotransmitter drugs and specify in the executive summary and results that these four medications are grouped together because of their mode of action related to GABA.



Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Page 24 Line 11 and multiple further instances	Discomfort. Dictionary definitions of discomfort imply that there is an element of pain. Pain is not how the majority of tinnitus patients describe their symptom. I think distress would be a more appropriate word. However, I won't be too upset if you disagree and want to keep it.	Authors and instruments vary in the terminology they use, with discomfort, distress and annoyance being common in the studies we reviewed; however, we are not aware of any clear distinctions in the meaning of these terms as they relate to the experience of tinnitus. In the text, the terms used by the authors of studies are often provided, but as explained in a footnote for the analytic framework, for any studies that used the terms 'discomfort', 'annoyance' or 'distress' to describe an outcome measure, these measures were initially included under the category label of 'discomfort.' Indeed, in the final version of the review, the two initial outcome categories for 'discomfort' and 'severity' were combined under the broader category heading of 'tinnitus-specific quality of life'.
Reviewer #5	Page 24 line 11	"In a rehabilitative context, discomfort from tinnitus is more often the reason for seeking medical attention than hearing loss". Is there any hard evidence to back up this statement? If so a reference should be supplied. If not, the statement should be removed.	The statement has been re-worded and references were added to back-up the revised statement.
Reviewer #5	Page 25 2nd paragraph	I realise that this was outside of the search parameters of this review but it might be worth inserting a new reference: there has been a huge international collaborative piece of work attempting to standardise tinnitus research and address many of the issues raised here. Landgrebe M, Azevedo A, Baguley D, Bauer C, Cacace A, Coelho C, Dornhoffer J, Figueiredo R, Flor H, Hajak G, van de Heyning P, Hiller W, Khedr E, Kleinjung T, Koller M, Lainez JM, Londero A, Martin WH, Mennemeier M, Piccirillo J, De Ridder D, Rupprecht R, Searchfield G, Vanneste S, Zeman F, Langguth B. Methodological aspects of clinical trials in tinnitus: a proposal for an international standard. J Psychosom Res. 2012 Aug;73(2):112-21.	The article was published after our search date. However, we have referenced this citation and a few others in our discussion section under "Future Research recommendations".

Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Page 27 Lines 7-8	I disagree that Acoustic coordinated reset neuromodulation (ACRN) is a Medical Intervention. I see it as a sound therapy. The team that developed it suggest that it is having profound action in the central nervous system but this assertion is largely speculative and extrapolated from separate research on Parkinson's disease. The ACRN device is a small signal generator and a set of headphones. It makes 4 tonal bleeps that the patient listens to. There is no evidence that it is anything more than just another sound therapy.	<p>We agree with the reviewer that the device itself is a signal generator; however, the optimization of the selection of the specific set of signals delivered in the treatment is determined based on patient-specific EEG parameters related to synchronization in the cortex. We grouped this treatment in the 'medical' category, but in its own sub-category because of the reliance on EEG to optimize the treatment. Other acoustic devices are typically recommended by audiologists based on considerations related to hearing test results, but they would not be qualified to conduct EEG testing of the sort needed to fit this device.</p> <p>Quote: "the therapeutic outcome might be optimized by further adapting the arrangement of the CR frequencies to the individual tonotopy and the dimensions of the pathological synchronized activity in the primary auditory cortex. Also, a closer meshed adaptation of the repetition rate F to the intrinsically varying _ peak frequency might possibly improve the therapeutic outcome." Tass, 2012, Pg 153</p>
Reviewer #5	Page 40 Line 8	It is true that in strict medical terms tinnitus is a symptom not a condition or disease. However, in common usage it most definitely is regarded as a condition. Even disease classifications regard it as an entity: it is H93.1 in the ICD-10 classification.	Thanks for the suggestion. We have added a reference to the introduction concerning the ICD usage and a quote to backup the statement that it is a symptom and not a disease, even though it may be commonly regarded as a condition.
Reviewer #5	Page 40 Lines 27-28	Traumatic brain injury is not a common cause of tinnitus. TBI certainly increases the Relative Risk of developing tinnitus but the vast majority of tinnitus patients have not had significant head injuries.	This statement was intended to refer to those in the military and this qualification has been added to the text. The statement now reads "Tinnitus is common in active-duty service members and veterans who have had traumatic brain injury (concussion) whether or not they have clinically significant hearing loss"



Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Page 43 Line 7	<p>"It is assumed that laser irradiation can improve cell proliferation, increase blood flow in the inner ear canal, and activate cellular activities that repair hair cells". Assumed is far too strong a word here.</p> <p>"It has been suggested" would be more appropriate. something like "various rationales for using laser therapy have been proposed but as yet remain unproven".</p>	<p>We modified the text to incorporate the concerns of the reviewer. It now says:</p> <p>Low level laser therapy (LLLTT) has been used to treat tinnitus. Various rationales for using laser therapy have been proposed but not yet validated. It is suggested that laser irradiation can improve cell proliferation, increase blood flow in the inner ear canal, and activate cellular activities that repair hair cells.³⁵ A variety of LLLT types have been used in patients and no specific dose recommendations exist regarding total energy density and method of application.</p>
Reviewer #5	Page 43 Line 24	"Transcranial magnetic stimulation (TMS) delivers an electrical field to the cerebral cortices". It doesn't. As its name suggests it delivers a magnetic field to the (superficial parts of the) cerebral cortices. This induces neuronal depolarisation.	We have replaced the word "electrical field with "electro-magnetic" filed. Descriptions of this therapy and in the Cochrane review suggest that the rTMS does induce electrical currents in the brain.
Reviewer #5	Page 43 Lines 31 to 49	Definitions and inclusions of CAM. As discussed previously, I do not think hyperbaric oxygen is CAM. I also query whether dietary exclusions are CAM.	We have moved hyperbaric oxygen and also dietary modifications to a separate category within medical interventions description.
Reviewer #5	Page 44 Lines 7-11	<p>This paragraph is no longer up to date and accurate. There is now a reasonable body of work supporting the use of cochlear implants in profound unilateral sensorineural hearing loss with associated severe tinnitus.</p> <p>For example: Punte AK, Vermeire K, Hofkens A, De Bodt M, De Ridder D, Van de Heyning P. Cochlear implantation as a durable tinnitus treatment in single-sided deafness. Cochlear Implants Int. 2011 May;12 Suppl 1:S26-9.</p>	Thank you for suggesting this reference. The text has been updated and now notes that these implants have also been used successfully to reduce tinnitus in subjects with single-sided deafness.
Reviewer #5	Page 44 Lines 23-31	This doesn't really explain what Neuromonics is. From this paragraph it sounds as if the counselling and support is the major component. This may in fact be true but it is not the premise used by Paul Davis, the inventor. For him, the sound is the chief component and the unique selling point (the counselling is effectively similar to TRT). The sound is a piece of chamber music that is individually spectrally altered to accommodate for each patient's hearing loss. The music has quite a large dynamic range such that there are noisy bits when tinnitus is usually drowned out and quieter bits when it is apparent.	Additional description has been added as suggested.

Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Page 46 Line 22 PICOTS	This is the first time this is mentioned in the document and as such the acronym should be explained as indeed it is on page 50, line 10. I know the paragraph below line 22 uses the various headings but I think (Population(s), Interventions, Comparators, Outcomes, Timing or followup, and Setting) should follow PICOTS here. Otherwise a new reader may head to his/her dictionary and find that a picot is an embroidery stitch!	We have provided explanation of the PICOTS term.
Reviewer #5		A comment rather than anything else: the review was critical of the complete lack of evidence to answer KQ3. I cannot see how KQ3 can even start to be addressed until KQ2 has been answered.	Thank you for the observation. We agree!
Reviewer #5	I re-performed the search and found a few studies that had not been included:	<ul style="list-style-type: none"> • Roberts C, Inamdar A, Koch A, Kitchiner P, Dewit O, Merlo-Pich E, Fina P, McFerran DJ, Baguley DM. A randomized, controlled study comparing the effects of vestipitant or vestipitant and paroxetine combination in subjects with tinnitus. <i>OtolNeurotol.</i> 2011 Jul;32(5):721-7. • Garin P, Gilain C, Van Damme JP, de Fays K, Jamart J, Ossemann M, Vandermeeren Y. <i>J Neurol.</i> 2011 Nov;258(11):1940-8. Epub 2011 Apr 21. Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation. • Muehlmeier G, Biesinger E, Maier H. Safety of intratympanic injection of AM-101 in patients with acute inner ear tinnitus. <i>AudiolNeurotol.</i> 2011;16(6):388-97. <p>Two of these feature experimental drugs that are not currently commercially available and this may be why they were not included. But the inclusion/exclusion criteria for KQ2 had no exclusions. So either the studies should be addressed or appropriate exclusions should be added.</p>	<p>All 3 papers were found in our search and considered for this review.</p> <p>Roberts, 2011: outcomes scores for THI & QIDS – crossover studies with no first period data</p> <p>Garin, 2011: change scores plotted with p-values (outcome scores not provided) – crossover study with no first period data</p> <p>Muehlmeier, 2011: outcome scores for THI-12 & self-reported loudness – this paper was excluded at title and abstract based on mixed population</p>
Reviewer #5	Pages 35, 154, 219, 276	Parazzini M, Del B, Jastreboff M, et al. Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators. <i>Int J Audiol.</i> 2011;50(8):548-53. EBSCO-CINAHL. Exclude: Comparators do not meet inclusion criteria. The second author's surname is Del Bo. His first name is Luca. So it should read Del Bo L,	The authors of this study pooled outcome data across treatment groups. This transformed the initial RCT design into an observational study without a comparator group. Studies without comparator groups were excluded from the review.



Commentator & Affiliation	Section	Comment	Response
Reviewer #5	Page 208	Kim NK, Lee DH, Lee JH, Oh YL, Yoon IH, Seo ES, Lee CH. Trials. 2010 Mar 28;11:34. Bojungikgitang and banhabaekchulchonmatang in adult patients with tinnitus, a randomized, double-blind, three-arm, placebo-controlled trial--study protocol. Marked as not a primary study. I agree that this should not be included but it does appear to be a primary study. It is a bizarre paper that has an extensive M&M section and possibly one of the most scientific designs of any tinnitus trial. And then no sign of the results. Weird! Would it be better marked as "Insufficient etc.."	The paper reports a study protocol and contains no outcome data.
Reviewer #5	Page 150, 206 272	Jalali MM, Kousha A, Naghavi SE, Soleimani R, Banan R. Med Sci Monit. 2009 Nov;15(11):PI55-60. The effects of alprazolam on tinnitus: a cross-over randomized clinical trial. Marked as Comparators do not meet inclusion criteria (page 206). I can't see what was wrong with the comparators. I can see that there is the usual crossover study criticism and only data prior to the crossover is really valid – and this hasn't been presented separately.	This study was captured in our search. We evaluated this study and it was a cross-over study with no first period data. As the reviewer noted, because there no pre-treatment data was provided, we excluded this study as it did not meet our eligibility criteria.
Reviewer #5	c. Methods	The methodology is appropriate.	Thank You.
Reviewer #5	d. Results	In places the amount of detail is rather overwhelming. However, this attention to detail is appropriate to this type of review. Many studies were excluded because the published paper had insufficient detail. It would have been possible to try and contact authors for more detail - though this would have added considerably to an already enormous workload. I have made a few points regarding missing studies in the attached file.	It is reasonable to contact authors. However, our experience has suggested that only for recent publications (within the last 2 years) will the authors reply to queries. We agree that this adds considerable workload as often the contact information of the authors is not current on the publications or they do not reply in a timely way.
Reviewer #5	e. Discussion/ Conclusion	The discussion and conclusion are appropriate.	Thank You.
Reviewer #5	f. Clarity and Usability	The report is well structured. I would question whether it is necessary to have such a large executive summary - it is approaching a third the size of the main review.	We agree with the reviewer, the executive summary has been revised.
Reviewer #6 (Public, anonymous)	a. General Comments	This is a well written manuscript that addresses important questions. The target population studies and the audience are explicitly defined and the key questions are clearly stated. Unfortunately, for the reasons discussed in the sections below, I don't believe the search review adequately answered the questions, and in spite of, or perhaps because of, the concise inclusion and exclusion criteria, I believe answers are not forthcoming and the reader can be led to improper conclusions without further explanation.	Thank You. We will address your comments below.



Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Public, anonymous)	b. Introduction	<p>This manuscript represents an ambitious project with the worthy objective of determining answers to three key questions regarding the comparative effectiveness of 1) methods used to identify patients for further evaluation and treatment, 2) medical/surgical, sound treatment/technological, or psychological/behavioral intervention (including combinations of interventions) and 3) identification of prognostic factors.</p> <p>The method of reaching these answers was to perform a systematic review of papers published between 1970 and 2012. A large number of peer reviewed articles (9,725) were reviewed but following exclusions, only 52 eligible publications were extracted for data.</p> <p>While this strict adherence to inclusion and exclusion criteria would typically yield valid conclusions to the key questions, two of the questions were not addressed since the data was deemed insufficient, and the response to the remaining key question (KQ2) concludes that the only intervention yielding a moderate strength of evidence is cognitive-behavioral therapy, while all pharmacological interventions improve either tinnitus related quality of life, or anxiety and depression symptoms.</p> <p>The search further concludes that the other medical interventions and sound technologies do not have sufficient strength of evidence for tinnitus related improvement. While the conclusions reached are valid based on methodology, I have concerns about some of the 52 articles that were included, the rationale for excluding some of the other articles, and the message the conclusions send to readers, some of whom could be agencies responsible for the promotion of tinnitus treatments. While this conclusion may in fact be a valid if the question was either “is there one treatment that is more effective than all others”, or “is there one treatment that is consistent in relieving the distress associated with tinnitus”, the conclusion that other approaches do not have a reasonable strength of evidence may not be valid if the selected articles were not truly representative of the body of scientific knowledge.</p> <p>Furthermore, the heterogeneity of the population comprising tinnitus sufferers may render the more common reliance on group versus individual data somewhat questionable.</p>	<p>The general topic of tinnitus went through the AHRQ's topic nomination process. During the separate topic refinement phase, we received input from key informants and finalized the key questions.</p> <p>The technical expert panel reviewed our search strategy. The strategy was then reviewed and approved by the investigative team that conducted this comparative effectiveness review.</p> <p>Yes, this summarizes the overall thrust of our review.</p> <p>We examine all citations that peer and public reviewers claim we missed in our literature search. If the reviewer feels we omitted important publications, then we would welcome a list of such publications to review.</p> <p>Thank you for the observation. We explored issues around applicability in our discussion.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Public, anonymous)	c. Methods	<p>This is the biggest concern I have with the manuscript. The search strategies are explicitly stated, but further explanations need to be provided concerning “risk of bias”, and “insufficient detail for aggregation of data”. For example, while only five articles met the criteria for inclusion into the review, at least one of them (the 2007 Davis article on Neuromonics) has a potential conflict of interest (the author was associated with Neuromonics) and I would assume that this would qualify for a “bias”.</p> <p>In addition, I am not clear what is meant by the statement that these are “head to head” studies. The treatments did not compare one sound treatment to another.</p> <p>Another potential bias due to a potential conflict of interest is (I believe) in the Tass article on acoustic coordinated reset modulation. I believe the author has created a product (which is a sound based tool and therefore, is probably placed in the wrong category (i.e. it is not a medical intervention, it is a sound based tool). These two studies, at least, likely have a high risk of bias, which should have excluded them.</p> <p>On the other hand, Appendix C listed numerous studies which were excluded because of “insufficient detail for aggregation of data” that are highly cited articles. The authors should explain what criteria define insufficient detail for aggregation of data. In addition, key question 3 (methods used to identify patients for further evaluation and treatment was unanswered because the “comparators did not meet the inclusion criteria”</p> <p>Articles defining the commonly used subjective scales for tinnitus, such as the Newman, et al article on the Tinnitus Handicap Inventory are utilized in clinical practice regularly so the excluding an article such as this or other articles by Kuk and Tyler on the Tinnitus Reaction Questionnaire may have been too strict an interpretation of the exclusion criteria that kept the authors from reaching important conclusions.</p>	<p>We have modified the text specified within the excluded list to indicate that the studies did not present measures of variance or presented proportions.</p> <p>Head to head studies are those that compare one treatment to another; the index treatment is not compared to a “no treatment” or placebo group. A synonymous term is to describe these studies as ones that use active comparators, but the comparator can be any other type of treatment.</p> <p>We explicitly state within the text the following: “The primary authors of the study have a contractual relationship with the manufacturer or hold shares within the company of the device and the study was funded by the manufacturers.” Sources of funding and investigator conflicts of interest were not reasons for exclusion, nor were they assessed in our risk of bias tools. Where possible, we report on the existence of potentially egregious conflicts of interest and let readers decide how much weight they should assign to such articles. Conflict of interest was not a reason for excluding studies.</p> <p>The reason for categorizing this treatment in the ‘medical’ category is not because it is a medical invention but because the optimization of the signal for the individual patient requires EEG testing.</p> <p>We have edited the text in the excluded list to provide greater clarity for why these studies were excluded. The primary reasons they were excluded is that the studies did not present a measure of variance around the mean estimate (and therefore we could not estimate an effect size) or the studies presented results only as the proportion of patients achieving a particular</p>



Commentator & Affiliation	Section	Comment	Response
			<p>change (i.e. recovered, not recovered).See also Appendix F.</p> <p>We assume the reviewer is referring to KQ1. If this is the case, the type of test used to assess management was not a reason for exclusion. Studies were excluded if they did not compare the effectiveness of different tools to determine candidacy for treatment.</p>
Reviewer #6 (Public, anonymous)	d. Results	<p>The amount of detail is excellent, and the Figures and Tables are appropriate. But again, I have some doubts about the validity of including some of the articles that were included, as well as why some of the articles that were excluded were placed in this category.</p> <p>Also, some of the newer sound treatments, Okamoto H. et al. PNAS 2010;107:1207-1210 and Zeng et al., Tinnitus Suppression by Low-Rate Electric Stimulation and its Electrophysiological Mechanisms. Hearing Research. 2011 Jul; 2007(1-2): 61-6 are not cited in either the included or excluded articles.</p>	<p>Okamoto: Insufficient detail for aggregation of data - retrieved and determined that data was not extractable for the purposes of this report.</p> <p>Zeng was excluded as it is a Case Series – this was excluded at the abstract stage and is not listed in our exclude list (only those at full text are recorded here). Full article was retrieved as a result of this query and status confirmed.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #6 (Public, anonymous)	e. Discussion/ Conclusion	While I think the authors appropriately cite the need for answering further questions, I am concerned that the criteria that selected only 52 of 9725 (.05%) may have chosen a less than satisfactory selection.	<p>A common tactic in the conduct of systematic reviews is to specify a wide initial search strategy to capture all important articles. This tactic creates a large 'signal to noise' ratio and is responsible for the sizable number of excluded studies in many reviews. Since many excluded studies do not actually have any direct connection to the topic at hand, a simple focus on the low proportion of included studies could be a misleading indicator of the validity of a search strategy.</p> <p>A more accurate reflection of a valid search strategy is the extent to which all relevant articles to answer the key questions are captured in the literature search.</p> <p>We have not been presented with any substantive evidence to suggest flaws in the search strategy we used to obtain articles to answer the three key questions. The search strategy was developed by an experienced medical librarian and reviewed by the technical expert panel.</p>
Reviewer #6 (Public, anonymous)	f. Clarity and Usability	<p>I think this report is well structured, but I fear policy makers may be misled into concluding that available treatments are not effective, a concept that would be disputed by the thousands of patients who receive improvement following treatments.</p> <p>That is not to say that the research in the area of tinnitus has been well designed, or that an abundance of "unscientific" articles have been published. So I think that if this report is to be published, the authors need to clarify their conclusions.</p>	<p>The evidence report clearly outlines our methods, results, and conclusions. Policy makers will be able to judge the utility of the report on their own and decide how much weight to attribute to the report during the decision making process.</p> <p>Our conclusions flow directly from our review of the evidence, which was based on methods reviewed by the TEP and approved by the authors. In response to peer and public review, we revised the report to improve clarity.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #7	a. General Comments	I read this extensive report with great interest. It is clear from the report that the reviewers found it difficult to categorize the interventions and I could not agree more. However, my area of expertise - CBT - is among the trickier to understand. Given the availability of a recent systematic review more detail could perhaps be included. On the other hand that would hardly change the conclusions.	We have tried to improve the explanation for categorizing studies in the CBT section. We appreciate the reviewer's comment that this is 'tricky' and that the conclusions would hardly change if slightly different choices had been made.
Reviewer #7	b. Introduction	A proper background to the field. The endorsement of the term subjective idiopathic tinnitus is a good choice. Perhaps there could be even more clear emphasis of the fact that most people with tinnitus do not suffer much from it and hence a treatment that makes a person less distressed is likely to make that person act as most people with tinnitus without changing the perceived loudness.	Thank you for your comment about the choice of the term 'subjective idiopathic tinnitus'. We have tried to convey the differences in thinking regarding the relative contributions of perceived loudness vs. distress throughout the report.
Reviewer #7	c. Methods	Yes and the search criteria as well. In particular this review does not endorse the odd idea of only analyzing tinnitus loudness as outcome (Cochrane)	Thank You.
Reviewer #7	d. Results	In my opinion the review is on the right level with some minor errors in table 23 were ACT is stated instead of ACI (the Henry study).	Thanks for spotting this typo. It has been corrected.
Reviewer #7	e. Discussion/ Conclusion	I agree with the suggestions for future research. Perhaps more detailed psychiatric classifications are needed as well.	This point has been added to the population research recommendations.
Reviewer #7	f. Clarity and Usability	Yes. It is about time to present the clear finding that psychological interventions are more robust than many medical interventions that are being practiced.	Thank You.
Reviewer #8	a. General Comments	<p>The report would not guide a clinician in determining which patients would benefit for a particular intervention.</p> <p>The report does not identify a target audience, which might be general practitioner, general ENT, specialist ENT, audiologist, clinical psychologist</p> <p>The key questions are reasonable</p>	<p>The McMaster EPC was charged with reviewing a body of evidence to address three specific key questions. Our final report is a reflection of the current state of the evidence relating to these questions. We agree with the reviewer that the current evidence is insufficient to guide medical practice.</p> <p>The report is not intended for a specific target audience. Any individual with an interest in the topic can consult the report,</p> <p>Thank you.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #8	b. Introduction	The (repeated) assertion that tinnitus triggers more medical consultations than hearing loss is unsubstantiated and dubious.	This statement has been re-worded and references provided. See responses to similar comments by other reviewers.
Reviewer #8	b. Introduction	Insufficient consideration is given to mechanisms.	The purpose of an evidence report is to address a series of key questions. Although some background information is provided in the introduction and the importance of a better understanding of mechanisms is also raised in the discussion, evidence reports do not have a mandate to provide substantive reviews of mechanisms of action related to health conditions or treatments.
Reviewer #8	b. Introduction	Some dubious citations are given - an example would be the American Tinnitus Association claiming that the majority of tinnitus is due to noise exposure.	It is expected that the perspectives of all stakeholders are considered in framing the problem and also that any grey literature that meets the criteria be included in the research that is reviewed. Given our mandate, it is not unreasonable to present the perspective of the ATA regarding noise being the most common attributed cause of tinnitus. The text also presents a range of other causes based on other references.
Reviewer #8	c. Methods	Satisfactory	Thank You.
Reviewer #8	d. Results	Satisfactory	Thank You.
Reviewer #8	e. Discussion/ Conclusion	The future research section contains some clear and robust recommendations for the trajectory that is needed and is commendable.	Thank You.
Reviewer #8	f. Clarity and Usability	Satisfactory	Thank You.
Reviewer #9	a. General Comments	Yes, the report is meaningful. There is some confusion on the target population. Authors make it clear results apply primarily to those patients over 50 years. It is likely that similar results will be found but not certain due to high relation between hearing loss and tinnitus in the older group and less so in the younger group.	Thank You. We agree that less is known about tinnitus in younger adults and that there is a need for further research pertaining to KQ3.
Reviewer #9	a. General Comments	The Key questions are well formulated and answered.	Thank You.

Commentator & Affiliation	Section	Comment	Response
Reviewer #9	a. General Comments	The main audience should be the primary care physicians as well as those audiologist and those who practice psychological therapies.	The report is not intended for a specific target audience. Any individual with an interest in the topic can consult the report. KQ1 in particular was intended to capture practices of primary care physicians, whereas KQ2 and KQ3 would apply more to specialist practitioners.
Reviewer #9	b. Introduction	The introduction is good. I don't feel that the association between hearing loss and tinnitus in younger people was explored in enough detail. The early work of SDG Stephens (Dai Stephens) and RRA Coles contains some work published in the British Journal of Audiology that might be useful to set the historical context, where the authors say that the evidence based (p103) approach was in its infancy. Their view of a stepped approach to management of tinnitus is probably still reasonably valid today. There was mention of cochlear implants being used to benefit those with severe tinnitus and often profound hearing loss in one or both ears. Maybe a word in the introduction about how one might ever be able to show evidence based benefit for such highly expensive and idiosyncratic approaches might be worth some introductory comments.	Thank you. These are interesting comments. We have consulted the suggested works and have added more information to the introduction about younger people. More has also been added to the introduction about the wide range of treatments offered for tinnitus, including the point about some treatments being extremely costly and highly individualized.
Reviewer #9	c. Methods	the inclusion and exclusion criteria are justiciable and good	Thank You.
Reviewer #9	c. Methods	search strategies are good	Thank You.
Reviewer #9	c. Methods	Statistical methods are appropriate - it is very difficult in this area of tinnitus research to find a good comparator. Another treatment is one possible here, wait list approach is also possible - with some restrictions for how long follow up can be. in general I don't think there was enough discussion about what might make worthwhile comparison.... however authors do comment in their recommendations.	The evidence report highlights the need for valid comparators based on the current state of the scientific evidence. The KQ were discussed with TEP and key informants.
Reviewer #9	c. Methods	outcomes are reasonably well documented	Thank You.
Reviewer #9	d. Results	The first section on KQ1 suggests that there are no studies that meet criteria for this question. However this does depend on what is being thought of as triage, differential diagnostic assessment or in depth diagnostic. If the stepped approach is taken in terms of a) those who might be able to self-manage, b) those who proceed to hearing assessment, c) manage their hearing loss with support, d) those who then manage tinnitus (which may then present differently) etc. there might be more literature available (or not, li haven't done the search to find out).	We agree with the reviewer that KQ1 could have been answered by studies looking at criteria for progressing from step to step in a staged approach; however, to be included in the present review, we were looking for papers that compared the effectiveness of different methods for determining who should proceed through which stages and we did not find research comparing the usefulness of different methods for this purpose.

Commentator & Affiliation	Section	Comment	Response
Reviewer #9	d. Results	the second section on KQ2 is well done and is relatively easy to read and understand. there could have been an analyses of analyses to combine the SE from different areas perhaps but I think this is catered for by the index of consistency that is used.	We agree that the index of consistency caters to this point. Given the available data, meta-analyses were not deemed to be appropriate (see comment to another reviewer regarding the feasibility of meta-analyses).
Reviewer #9	d. Results	The third section on KQ3 is disappointing but right.	Thank You.
Reviewer #9	e. Discussion/ Conclusion	<p>Implications are well stated and limitations described excellently. It may not be the authors job but i think that there may be some hesitancy in how to proceed with best practice or good practice following the review especially in the under 50s. Hence it might be good to direct people to good practice and ask them to use output from this to prioritize their current practice.</p> <p>The future research is well stated -li think there does need to be a better way to be able to interpret and use previous treatment history (self-management etc....) and to indicate such using systematic definition would be good. i think that there should be more emphasis on the impact of tinnitus on family and carers - a point that is not raised here.</p> <p>There is lack of clarity in the executive summary and in the main text eg p97 on what the relative self-referral or referral of people with tinnitus and people with hearing loss and people with both. Clearly those with moderate or severe tinnitus have a much greater impact of on their QoL than for moderate hearing loss - therefore there is a higher self and primary care referral rate for diagnosis and treatment. This is part of KQ1 and research around this might be strengthened as self referral for either is very low!</p>	<p>A comparative effectiveness review summarizes and discusses the evidence for the key questions. Formulation of clinical practice and health policy guidelines is beyond the scope of the review.</p> <p>We agree that family and caregiver issues are important to consider the provision of health care. However, these issues were beyond the scope of this report.</p> <p>Hopefully our rewrites have made this section clearer for the reader.</p>
Reviewer #9	f. Clarity and Usability	<p>Yes it is well structured.</p> <p>The conclusions do not form a sufficient base to form a clear policy for what should be done at this moment but offer moderate support for CBT and other psychological therapies in the groups of patients show here who refer themselves or who are referred.</p>	Thank You.
Reviewer #9		Practice decisions can possibly be guided by the work and should use the work proactively to question their clinical practice.	Thank You.
Reviewer #10	a. General Comments	The objectives of this review were clearly stated and met. The report will be extremely useful to researchers and clinicians interested in evidence-based practice in tinnitus care.	Thank You.



Commentator & Affiliation	Section	Comment	Response
Reviewer #10	b. Introduction	<p>“Cochlear implants may reduce tinnitus because the tinnitus is masked by improving the perception of external sounds or through electrical stimulation of the auditory nerve, but are only appropriate for use by a very specific subset of patients (e.g., people who have bilateral profound sensory-neural hearing loss).36”</p> <p>COMMENT: CIs are being used for treatment of tinnitus in patients with SSD although this use would be considered “off label” www.sbccc.org.br/arquivos/LG_07-2011_the-effects-of-unilateral.pdf</p>	Excellent point. The text now includes the use of cochlear implants for tinnitus in people with single-sided deafness and the suggested reference as well as another have been added.
Reviewer #10		<p>“However, various pharmacological treatments, including antidepressants, anxiolytics, vasodilators and vasoactive substances, and intravenous lidocaine, have been prescribed for tinnitus.23-27 See Table 1 for examples. These treatments have been indirect solutions because they focus on tinnitus-associated symptoms, such as depression symptoms, stress, or sleep disturbance”</p> <p>COMMENT: Lidocaine is used to directly reduce tinnitus but is not a clinically viable solution due to short-term effectiveness and adverse effects.</p>	Noted with thanks.
Reviewer #10	c. Methods	Yes to all questions.	Thank You.
Reviewer #10	d. Results	<p>Yes to all questions with the possible exception of “Did they include studies that ought to have been excluded?”</p> <p>There are two studies cited in which potential COI exists:</p> <p>1) Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: Double-blind study. RevistaBrasilOtorrinolaringol. 2005;71(5):618-23. PMID:16612523</p> <p>The two authors of this study hold the patent on use of acamprosate for tinnitus: www.freshpatents.com/-dt20100715ptan20100179220.php</p> <p>2) Davis PB, Paki B, Hanley PJ. Neuromonics tinnitus treatment: Third clinical trial. Ear Hear. 2007;28(2):242 PubMed -59. PMID:17496674</p> <p>The lead author on this paper is the inventor of Neuromonics and continues to work a consultant for the Neuromonics company.</p>	<p>We have added some explanation about the general issue of conflict of interest in the discussion under CER limitations.</p> <p>We have noted this in the text of the results.</p> <p>We have noted this in the text of the results.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #10	e. Discussion/ Conclusion	Yes to all questions.	Thank You.
Reviewer #10	Under Future Research Recommendations> Population	<p>It may be premature to include consideration of ethnicity as a controlled subject variable in all investigations of tinnitus.</p> <p>I know of no research that suggests a genetic susceptibility to developing tinnitus – although hearing loss and mood disorders can have a hereditary component, tinnitus onset is typically attributed to exogenous factors such as noise exposure, head/neck injury, drugs, trauma, etc.</p> <p>It is possible that cultural biases could play a role in neuroemotional and neurocognitive influences tinnitus awareness or distress; however, until this has been formally investigated, recommending that ethnicity be included as a controlled variable could unnecessarily complicate future tinnitus research.</p>	Our recommendation regarding ethnicity comes out of the drive to include ethnic diversity in research studies
Reviewer #10	f. Clarity and Usability	Yes to all questions.	Thank You.
Reviewer #11		The report is clinically meaningful, the target population and audience are explicitly defined, the key questions are all clear.	Thank You.
Reviewer #11		The introduction clearly outlines the issues to be addressed and provides the context for the balance of the report	Thank You.
Reviewer #11		The inclusion and exclusion criteria are well defined and justified.	Thank You.
Reviewer #11		The statistical methods are generally appropriate but one exception is discussed in the attached file	Thank You.
Reviewer #11		<p>The report includes, appropriately, a large volume of material, that is very well organized, based on the question being addressed and then the sub-questions.</p> <p>In addition to locating, coding, and organizing a vast amount of data, they applied important and appropriate criteria (such as risk-of-bias) tables to assign appropriate value to these studies.</p>	Thank You.
Reviewer #11		<p>The implications are clearly stated and appropriate (one exception is discussed in the attached file).</p> <p>Future directions are discussed in very good detail, which includes a well organized outline for future research</p>	Thank You.

Commentator & Affiliation	Section	Comment	Response
Reviewer #11		<p>The report manages to take a large volume of data and put it into context, but imposing an organization on the questions and then reviewing the studies in the context of this organization.</p> <p>The conclusions, especially that more research is needed, are well justified and articulated. One exception is noted in the attached file.</p>	Thank You.
Reviewer #11		In almost all key respects this is a clearly written report.	Thank You.
Reviewer #11		The authors had to make many difficult decisions about synthesizing data from multiple studies. These decisions are in areas where experts sometimes disagree, and for the most part the authors justified their decisions (and I also agree with their judgment calls).	Thank You.
Reviewer #11		For example, in deciding on the quality of the evidence they gave a lot of weight to risk-of-bias tables, they did not use summary quality scores (again, I agree).	Thank You.
Reviewer #11		<p>One of the more difficult decisions the authors had to make was what to do when there are only a few studies that address a question, and the results of these studies are (or may be) heterogeneous.</p> <p>They decided to present a forest plot but not to report a summary effect. The authors may have felt that a summary effect would lend itself to misinterpretation, and they are probably correct about that.</p>	Thank You.

Commentator & Affiliation	Section	Comment	Response
Reviewer #11		<p>However, they seem to have applied this rule across all analyses, including some where the results do appear to be consistent across studies. In some of these cases, the summary effect is clinically important and statistically significant.</p> <p>For example, Figure 19 (top section) includes 10 studies that looked at the impact of CBT/CBT combination on depressive symptoms. The authors note that only one of these is statistically significant. However, if they had performed a meta-analysis they would have found that there is no evidence of heterogeneity (all of the observed dispersion can be attributed to random error) and the summary effect is -.408 with a confidence interval of -.605 to -.212. The p-value is less than .001. (This assumes that the data listed for each study is independent, but the results would probably be similar if there is some overlap among the “Henry” studies)</p> <p>Similarly, Figure 20 (top section) includes five studies that looked at the impact of psychological and behavioral interventions on global outcomes. The authors note that only one of these is statistically significant. However, if they had performed a meta-analysis they would have found that there is no evidence of heterogeneity (all of the observed dispersion can be attributed to random error) and the summary effect is 0.33 with a confidence interval of 0.08 to 0.58. The p-value is less than .01.</p> <p>It seems the same would be true for some of the other sets of studies as well.</p> <p>In effect, the authors say that the studies show no evidence of an effect, and even if they did, the studies are flawed. In fact, though, there is evidence of an effect. We also need to see if the studies are flawed, but now this becomes a more serious question and one that requires more deliberation.</p> <p>This is especially so since there may be evidence here that some of the treatments do work for ameliorating some of the symptoms. Given the dearth of good options, this cannot be dismissed out of hand.</p>	<p>In some cases the results were consistent; however, the interventions, comparators, and outcome measures were still heterogeneous enough to suggest that pooling the studies would inaccurately create the impression that the strength of evidence was greater than it really was.</p> <p>The studies are not independent as several studies had multiple treatment arms. We have added some comments in the methods to address this.</p> <p>A meta analysis would have obscured the fact that the studies exhibited substantial clinical heterogeneity with respect to populations, interventions, comparators, outcomes, and lengths of follow-up. Due to these substantial differences, the strength of evidence for most results was rated as low or insufficient. While some individual studies do suggest that some specific interventions have some impact on some tinnitus outcomes, a meta analysis in this report would lead readers away from the true state of the evidence. This ‘state’ is that tinnitus research to date is composed of a patchwork of different interventions that generally do not have an impact on the condition. In cases where some impact is evident, the strength of evidence is low or insufficient for us to conclude that the studies are reporting true effects.</p>

Commentator & Affiliation	Section	Comment	Response
Reviewer #11		<p>In general, the report does not make full use of the opportunities afforded by meta-analysis, choosing instead to work with narrative reviews for each set of studies.</p> <p>The authors repeatedly make the point that many of the studies are under-powered, and then go on to report that none were statistically significant. This is one of the reasons why we use meta-analysis. It can work synthesize results from a series of under-powered studies. In the two examples above, the summary effect is statistically significant and clinically important despite the fact that each study was under-powered.</p> <p>The authors also argue that the studies should not be synthesized because the effect size varied. While this is true in some cases, in the two examples cited above there is no evidence of heterogeneity. In fact, tau-squared (the variance of true effects) is zero.</p> <p>In sum, while the authors have done an exemplary job of locating studies, organizing them, and summarizing the results of individual studies, they elected not to perform a meta-analysis. The figures suggest that meta-analysis may actually show that some interventions are effective for treating some symptoms. While this would not affect the key conclusion, that more research is needed, it might provide some direction for clinicians and patients in the meantime.</p>	<p>One of the primary reasons to not undertake meta-analysis are concerns with clinical heterogeneity. Although we grouped studies by the types of interventions, these were by no means free of clinical heterogeneity. For example, all the CBT interventions were in fact quite diverse in the type of treatment, dose and follow-up. The types of patients were also heterogeneous. Similarly, the grouping of antidepressants were in fact 4 different drugs with differing doses. Similarly, the doses used for the rTMS studies and the locations were so markedly different, we thought these to be too heterogeneous to combine. These examples show the clinical rationale for not pooling effect estimates. Chapter 2 describes our methods and we describe that clinical heterogeneity is the primary reason for not presenting summary estimates. We do not indicate that the effect sizes and the lack of power motivated our decision not to pool study estimates.</p> <p>We based our decision for not providing a pooled estimate on clinical and methodological heterogeneity across studies and not on statistical heterogeneity because there were grouping in CBT section where statistical heterogeneity was negligible.</p>