



Effective Health Care Program

Comparative Effectiveness Review
Number 122

Evaluation and Treatment of Tinnitus: Comparative Effectiveness



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Comparative Effectiveness Review

Number 122

Evaluation and Treatment of Tinnitus: Comparative Effectiveness

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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We would also like to thank those who worked so conscientiously retrieving and screening citations, abstracting data, preparing figures, and editing the report: Julianna Beckett, Judy Brown, Amy Bustamam, Patricia Carson, Bryan Cheeseman, Roxanne Cheeseman, Louise Don-Wauchope, Angela Eady, Mary Gauld, Suzanne Johansen, Sara Kaffashian, Meghan Kenny, Leah Macdonald, Maureen Rice, Carrie Sniderman, Rob Stevens, Marroon Thabane, and Ian White. Our thanks to Harry Shannon and Nancy Santesso for providing statistical assistance along the way.

Thank you to our Peer Reviewers for the thoughtful comments.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Structured Abstract

Objectives. A review was undertaken to evaluate the peer-reviewed literature on three areas of tinnitus management for the following Key Questions (KQs): (1) measures used to assess patients for management needs (KQ1); (2) effectiveness of treatments (KQ2); and (3) identification of prognostic factors (KQ3).

Data sources. MEDLINE[®], Embase[®], CINAHL[®], PsycINFO[®], AMED[®], and Cochrane CENTRAL were searched from January 1970 to June 2012. An extensive grey literature search, which included documents from regulatory and tinnitus-related organizations, was also undertaken.

Review methods. Standardized systematic review methodology was employed. Eligibility criteria included English-language studies of adults with subjective idiopathic (nonpulsatile) tinnitus; excluded studies involved tinnitus as the result of middle-ear pathologies or focused on methods to determine psychosomatic tinnitus. For KQ2, all pharmacological/food supplement, medical/surgical, sound/technological, and psychological/behavioral interventions aimed at ameliorating tinnitus symptoms were eligible (except stapedectomy or tympanoplasty). Randomized controlled trials with placebo controls or head-to-head trials were eligible for all KQs.

Results. From 9,725 citations, 52 eligible publications were extracted for data. None were eligible for KQ1 or KQ3. From the 52 publications eligible for KQ2, 17 evaluated pharmacological interventions; 11 evaluated medical interventions (low-level laser, acupuncture, transcranial magnetic stimulation); 5 evaluated sound technologies; and 19 evaluated psychosocial/behavioral interventions. Data on adverse effects were generally poorly collected and reported.

Conclusions. There is low strength of evidence (SOE) indicating that cognitive behavioral therapy interventions improve tinnitus-specific quality of life relative to inactive controls. For pharmacological interventions, SOE is low for improvements to subjective loudness from neurotransmitter drugs versus placebo; insufficient for antidepressants, other drugs, and food supplements with respect to subjective loudness; and insufficient for all other outcomes. There is insufficient SOE to suggest that medical interventions improve outcomes relative to inactive controls; sleep and global quality of life were not evaluated for medical interventions. The SOE for the adverse effect of sedation in pharmacological studies was judged insufficient. Future research should address the substantial gaps identified for KQ1 and KQ3. For KQ2, future research should concentrate on improving collection of adverse effects, calculating sample size, and specifying doses for interventions.

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Executive Summary

Background

Tinnitus is the perception of sound in the absence of an external auditory stimulus; as such, tinnitus is a symptom, not a disease. An estimated 16 percent of the American population (50 million people) experience tinnitus, with up to 16 million seeking medical help and 2 million being unable to lead a normal life.¹ The prevalence of tinnitus increases with age and noise exposure.^{2,3} Additionally, tinnitus is an increasing problem in more recent birth cohorts.⁴

A variety of conditions and experiences can lead to tinnitus, but the exact physiology is still unknown. Patients are often described as presenting with symptoms of either objective or subjective tinnitus. Objective tinnitus is perceptible by patients and examiners. Subjective tinnitus is perceptible only by patients, yet is not due to a hallucination. Both forms of tinnitus may or may not be idiopathic. Some investigators have argued that tinnitus should be classified by origin, either as somatic or neurophysiologic.⁵ In this review, we will use the term *subjective idiopathic tinnitus*, rather than neurophysiologic tinnitus, because it is the term most commonly used in the current literature. Subjective idiopathic tinnitus is also the most commonly diagnosed type of tinnitus.⁶

Treatments for subjective idiopathic tinnitus are wide ranging in scope and may include medical/surgical treatments, sound treatments/technologies, and psychological/behavioral treatments. For the present review, treatment groups revolve around four main categories of intervention: pharmacological or food supplement, medical/surgical, sound technology, and psychological/behavioral.

Scope and Key Questions

Standardized guidelines for the diagnosis and treatment of tinnitus do not exist in the United States. To help inform medical practice, this systematic review was undertaken to explore prognostic factors and strategies for the optimal management of tinnitus. Three Key Questions (KQs) governed the review:

KQ1. In patients with symptoms of tinnitus (ringing in the ears, whooshing sounds, etc.), what is the comparative effectiveness of methods used to identify patients for further evaluation or treatment?

KQ2. In adults with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral interventions, including combinations of interventions?

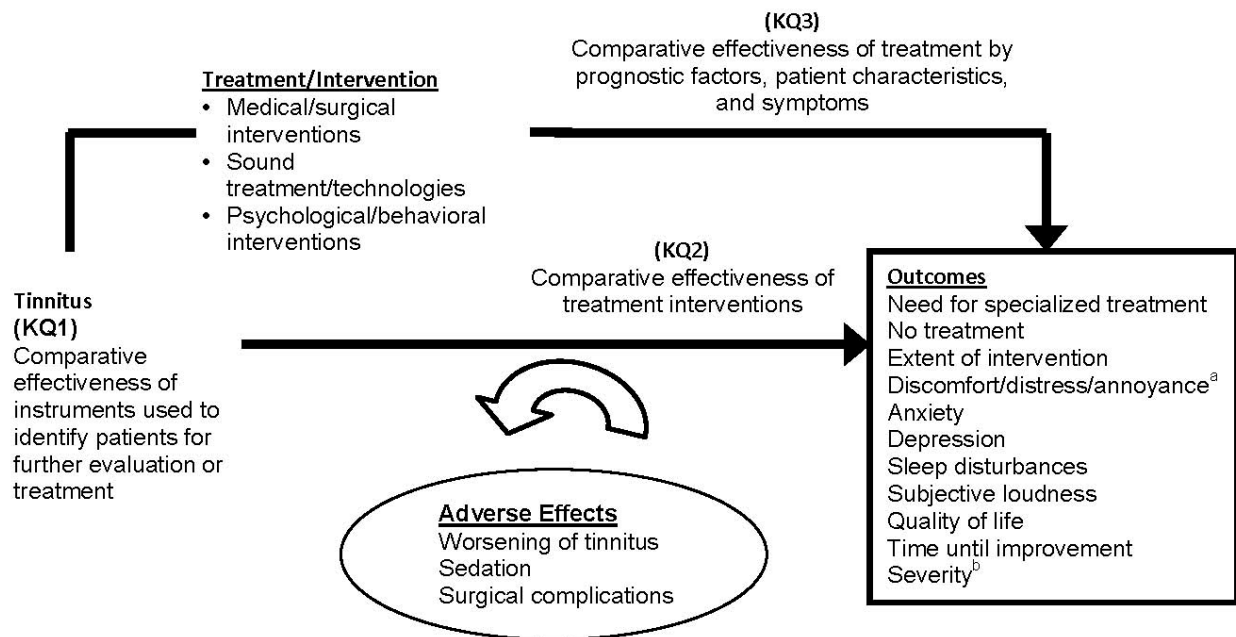
KQ3. For adults with subjective idiopathic tinnitus, what prognostic factors, patient characteristics, and/or symptom characteristics affect final treatment outcomes?

Analytic Framework

Following consultation with Key Informants, the Agency for Healthcare Research and Quality (AHRQ) Task Order Officer, and the investigative team, key research questions were

developed. Figure A shows a flow diagram indicating the relationship between research questions in this comparative effectiveness review (CER). This framework depicts the KQ as outlined in the PICOTS (population(s), interventions, comparators, outcomes, timing or followup, and setting) format. The PICOTS components for each KQ are provided in full detail in Table A.

Figure A. Analytic framework



Abbreviation: KQ = Key Question

^aAny studies that used the terms “annoyance” or “distress” to describe their outcomes were included under the category of “discomfort.”

^bThe outcome “severity” was added during data extraction. As severity was an outcome reported in 18 of 34 papers, it was decided that it should not be collapsed into any other outcome category.

Methods

Search Strategy

The search was conducted in six databases—MEDLINE[®], Embase[®], Cochrane CENTRAL, PsycINFO[®], AMED[®], and CINAHL[®]—as well as the grey literature, from January 1970 to June 2012. The search strategy used medical subject headings (MeSH[®]), keywords, and text words, including “tinnitus” and “humans not animals,” with a limit to English-language citations. The search also included the following Web sites: American Tinnitus Association, Association for Research in Otolaryngology, American Academy of Audiology, Emory University Tinnitus and Hyperacusis Center, Tinnitus Research Initiative, and Deafness Research UK. Reference lists of eligible studies were also reviewed at full-text screening.

Criteria for Inclusion/Exclusion of Studies in the Review

Included studies had to be randomized controlled trials (RCTs) or observational studies with true control groups (e.g., cohort, case control). For KQ2 and KQ3, included studies had to evaluate tinnitus treatments. Studies were excluded when tinnitus resulted from middle-ear

pathologies (mechanics, otitis media, otosclerosis, etc.), when interventions were stapedectomy or tympanoplasty, or when interventions were focused on determining whether patients had psychosomatic tinnitus. See Table A for inclusion and exclusion criteria.

Data Extraction, Assessment of Risk of Bias, and Applicability

Standardized and validated scales were used (the Newcastle-Ottawa quality assessment scales for case-control studies and cohort studies,⁷ and the Jadad scale for RCTs⁸) to assess risk of bias. Two raters evaluated the studies using standardized assessment forms, and disagreements were resolved through consensus. Applicability⁹ was assessed by considering comorbidities (psychological or related to hearing loss), ages of subjects, locations where study subjects were recruited, specific treatment providers, and lengths of time to treatment.

Data Synthesis and Strength of Evidence

All included studies were summarized in narrative form and stratified by the different outcomes and interventions. Interventions were organized into four main categories: pharmacological or food supplement, medical, sound technology, and psychological/behavioral. Meta-analysis was not undertaken due to the clinical heterogeneity of the interventions and outcomes; however, standardized mean differences were estimated for each study and presented in forest plots to compare effect sizes across studies. Two reviewers based their assessments of the overall strength of evidence (SOE) on AHRQ’s “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.”^{10,11}

Table A. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	<p>KQ1: Adult (≥18 years) patients who visit health care practitioners with symptoms of tinnitus (ringing in the ears, whooshing sounds, etc.)</p> <p>KQ2 & KQ3: Adults (≥18 years) with a diagnosis of subjective idiopathic (nonpulsatile) tinnitus who are sufficiently bothered by tinnitus that they are seeking a treatment intervention</p> <p>No restriction on the length of time of symptoms</p>	<ul style="list-style-type: none"> • Subjects <18 years of age • Dx of pulsatile tinnitus • Unilateral cases with specific medical dx (e.g., paraganglioma, acoustic neuroma) • Tinnitus as side effect of drugs • Nonhuman

Table A. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Interventions	<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 (THI, TRQ, TSI, VAS, etc.)</p> <p>KQ2: Any treatment/therapy used to reduce/help cope with tinnitus, including but not limited to the following:</p> <p>Medical/Surgical</p> <ul style="list-style-type: none"> • Pharmacological treatments: <ul style="list-style-type: none"> • Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, and trimipramine) • Selective serotonin-reuptake inhibitors: fluoxetine and paroxetine • Other: trazodone; anxiolytics (e.g., alprazolam); vasodilators and vasoactive substances (e.g., prostaglandin E1); intravenous lidocaine; gabapentin; Botox (botulinum toxin type A); and pramipexole) • Laser treatments • TMJ treatment: dental orthotics and self-care, surgery • Transcranial magnetic stimulation • Hyperbaric oxygen therapy • Complementary and alternative medicine therapies: Gingko biloba extracts; acupuncture; diet, lifestyle, and sleep modifications (caffeine avoidance, exercise) <p>Sound Treatments/Technologies</p> <ul style="list-style-type: none"> • Hearing aids, cochlear implants, sound generators, maskers • Neuromonics <p>Psychological/Behavioral</p> <ul style="list-style-type: none"> • Cognitive behavioral therapy, biofeedback, education, relaxation therapies, Progressive Tinnitus Management, tinnitus retraining therapy <p>Combination Therapies</p> <ul style="list-style-type: none"> • Any combination of tinnitus interventions (e.g., pharmacological treatment with cognitive behavioral therapy) <p>KQ3: Any treatment/therapy used to reduce/help/cope with tinnitus, including but not limited to those described in KQ2</p>	<p>KQ1: Nondirect observations</p> <p>KQ2: No exclusions for interventions</p> <p>KQ3: No exclusions for interventions</p>

Table A. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Comparators	<p>KQ1: Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus</p> <p>KQ2: Placebo, no treatment, wait list, treatment as usual, other intervention/treatment with control</p> <p>KQ3:</p> <ul style="list-style-type: none"> • Prognostic factors: length of time to treatment after onset, audiological factors (degree and type of hearing loss, hyperacusis, loudness tolerance, masking criteria, etc.), head injury, anxiety symptoms, mental health disorders, and duration of tinnitus • Patient characteristics: age, sex, race, medical or mental health comorbidities, socioeconomic factors, noise exposure (environmental, recreational, and work related [including active and past military duty, and occupational hazards]), involvement in litigation, third-party coverage • Symptom characteristics: origin/presumed etiology of tinnitus, tinnitus duration since onset, subcategory of tinnitus, severity of tinnitus 	<p>KQ1: No exclusions</p> <p>KQ2: No comparator/control</p> <p>KQ3: No exclusions</p>
Outcomes	<p>KQ1: Final outcome: no treatment, need for specialized treatment (e.g., audiology, otolaryngology, neurology, mental health care), extent of intervention</p> <p>KQ2: Sleep disturbance, discomfort, anxiety symptoms, depression symptoms, subjective loudness, quality of life, tinnitus severity, adverse effects (worsening of tinnitus, sedation, surgical complications)</p> <p>KQ3: Time until improvement, sleep disturbance, discomfort, anxiety symptoms, depression symptoms, subjective loudness, quality of life, return to “normal” work, adverse effects (worsening of tinnitus, sedation, surgical complications)</p>	No exclusions
Publication language	English	Non-English
Study design	<p>All KQs: RCTs or observational studies with true control groups (e.g., cohort studies, case-control studies)</p> <p>All KQs: Original research studies providing sufficient detail about methods and results to enable use and aggregation of the data and results</p> <p>All KQs: Possibility of extracting relevant outcomes from data in the papers</p> <p>Controlled experimental studies (manipulation of treatment)</p>	<ul style="list-style-type: none"> • Systematic reviews and narrative reviews (excluded but pulled for full reference list review), case reports/studies, and case series • Editorials, comments, letters, opinion pieces, abstracts, and Webcasts
Setting	All KQs: Primary care, specialty care (audiology, otolaryngology, neurology, mental health), university research, Internet	No exclusions

Table A. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Other criteria	Studies must address 1 or more of the following for tinnitus: KQ1: Instruments used to identify patients for further evaluation or treatment KQ2: Treatment modality KQ3: Predictors of treatment outcomes (prognostic factors, patient characteristics, and symptom characteristics)	No other exclusions

Abbreviations: Dx = diagnosis; KQ = Key Question; RCT = randomized controlled trial; THI = Tinnitus Handicap Inventory; TMJ = temporomandibular joint; TRQ = Tinnitus Reaction Questionnaire; TSI = Tinnitus Severity Index; VAS = visual analog scale

Peer Review and Public Comment

Experts in audiology, epidemiology, and medical specialties, and researchers and individuals representing stakeholder and user communities were invited to provide external peer review of this CER. The AHRQ Task Order Officer and an associate editor also provided comments on the report. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. All reviewer comments were considered and the text revised. A disposition-of-comments report will be made available on the AHRQ Web site 3 months after the posting of this final report.

Results

The initial literature search yielded 9,725 citations; 834 citations (8.6 percent) passed title and abstract screening. From the studies screened at full text, 52 eligible publications were extracted for data. None were eligible for KQ1 or KQ3.

KQ1. In patients with symptoms of tinnitus (ringing in the ears, whooshing sounds, etc.), what is the comparative effectiveness of methods used to identify patients for further evaluation or treatment?

No studies were found to address this KQ.

KQ2. In adults with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral interventions, including combinations of interventions?

Pharmacological or Food Supplement Interventions

A total of 17 articles¹²⁻²⁸ reported on 16 unique studies that evaluated interventions in the pharmacological or food supplement domain (Table B). Five articles¹²⁻¹⁶ investigated antidepressant drugs versus placebo. These drugs included sertraline,^{12,13} paroxetine,¹⁴ trazodone,¹⁵ and nortriptyline.¹⁶ Dosage levels in the sertraline, paroxetine, and nortriptyline articles were at the recommended levels for treating depression. However, the dosage level in the trazodone study was below the recommended dose for depression; the dosage level was instead suitable for use as a sleep aid. Five publications¹⁷⁻²¹ examined neurotransmitter drugs, which stimulate or enhance γ -aminobutyric acid (GABA), versus placebo. The neurotransmitter drugs were gabapentin,¹⁷ baclofen,¹⁸ alprazolam,¹⁹ and acamprosate.^{20,21} Three studies investigated other drugs, including methylprednisolone versus placebo,²² vardenafil versus placebo,²³ and

Deanxit versus placebo (with each participant given 1 mg clonazepam in addition to Deanxit or placebo).²⁴ Four papers evaluated food supplements, with two^{25,26} focused on Gingko biloba, one²⁷ on zinc, and one²⁸ on honeybee larvae. All food supplements were compared with placebo (which was hydrogenated dextrin in the larvae study). All of the studies were RCTs.

Adverse effects spanned a range of clinical severity, from dry or sour mouth^{14,15} to confusion,¹⁸ but generally subsided after discontinuation of treatment. Four studies^{14,15,18,19} reported symptoms of sedation (sleepiness, drowsiness) during the use of antidepressants (trazodone and paroxetine) and neurotransmitter drugs (baclofen, alprazolam). The findings for sedation were inconsistent and imprecise, as estimates of affected patients were poorly characterized; the SOE for sedation was insufficient in patients with tinnitus.

Table B. Summary of findings for Key Question 2: pharmacological or food supplement interventions

Outcome	# of Articles	Overall Strength of Evidence	Comment
Tinnitus-specific quality of life	13 ^{12-14,16-18,21-26,28}	Insufficient for antidepressants, neurotransmitter drugs, food supplements, and other drugs	Although nortriptyline, sertraline, acamprosate, and Deanxit were shown to produce some improvement in tinnitus-specific quality of life, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of moderate risk of bias and inconsistent and imprecise effect estimates.
Subjective loudness	9 ^{12,13,18-20,22,24,26,27}	Low for neurotransmitter drugs Insufficient for antidepressants, food supplements, and other drugs	Evidence suggests that neurotransmitter drugs showed improvement in subjective loudness vs. placebo; however, because of moderate risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. Only single studies of Deanxit, methylprednisolone, zinc, Gingko biloba, and sertraline showed improvements in subjective loudness compared with placebo. Based on single studies of each comparison, there is insufficient evidence to determine whether these findings represent true effects.
Sleep disturbance	3 ^{14,23,24}	Insufficient for antidepressants and other drugs	The strength of evidence is insufficient to conclude whether paroxetine, vardenafil, and Deanxit showed improvements in subjective loudness compared with placebo. Only single studies of paroxetine and vardenafil reported improvements in sleep disturbance vs. placebo, and no improvement was observed with Deanxit. Based on single studies of each comparison, there is insufficient evidence to determine whether these findings represent true effects.
Anxiety symptoms	4 ^{12-14,16}	Insufficient for antidepressants	The strength of evidence is insufficient to conclude whether sertraline, paroxetine, and nortriptyline showed improvements in anxiety symptoms compared with placebo. Only single studies comparing sertraline, paroxetine, or nortriptyline with placebo reported improvements in anxiety symptoms, with differences statistically significant only for sertraline. Based on single studies of each comparison, insufficient evidence exists to conclude whether these findings represent true effects

Table B. Summary of findings for Key Question 2: pharmacological or food supplement interventions (continued)

Outcome	# of Articles	Overall Strength of Evidence	Comment
Depression symptoms	6 ^{12-14,16,24,28}	Insufficient for antidepressants, food supplements, and other drugs	<p>The strength of evidence is insufficient to conclude whether sertraline, paroxetine, nortriptyline, honeybee larvae, and Deanxit showed improvements in depression symptoms compared with placebo.</p> <p>Although studies of sertraline, paroxetine, and nortriptyline reported improvements in depression symptoms vs. placebo, not all differences were statistically significant, the risk of bias was moderate, and effects were inconsistent.</p> <p>Only single studies evaluated Deanxit and honeybee larvae. Based on single studies for each of these interventions, insufficient evidence exists to conclude whether these findings represent true effects.</p>
Global quality of life	6 (2 papers from the same study addressed sertraline) ^{12-15,20,23,25}	Insufficient for antidepressants, food supplements, and other drugs	<p>The strength of evidence is insufficient to conclude whether sertraline, paroxetine, trazodone, acamprosate, vardenafil, and Ginkgo biloba showed improvements in global quality of life compared with placebo.</p> <p>Although sertraline showed improved global quality of life vs. placebo, the evidence is insufficient to conclude whether the findings represent true effects because of moderate risk of bias, and inconsistent and imprecise effect estimates.</p> <p>Only single studies evaluated acamprosate, vardenafil, and Ginkgo biloba. Based on single studies for each of these interventions, insufficient evidence exists to conclude whether these findings represent true effects.</p>

Note: Deanxit comparison is a crossover trial of Deanxit vs. placebo, with each participant given 1 mg clonazepam in addition to Deanxit or placebo; honeybee larvae comparator is hydrogenated dextrin.

Medical Interventions

Eleven studies were included for medical interventions in KQ2 (Table C). Six²⁹⁻³⁴ of these evaluated repetitive transcranial magnetic stimulation (rTMS) or electromagnetic stimulation; three evaluated low-level laser therapy (LLLT);³⁵⁻³⁷ and one each evaluated acupuncture³⁸ and acoustic coordinated reset neuromodulation (ACRN) therapy.³⁹ All the studies in the medical intervention group have small sample sizes (n<60).

Adverse effects were not consistently reported or specified in the methods of the studies. None of the studies in the medical interventions group reported dropouts related to adverse effects. In general, adverse effects were transient and mild.

Table C. Summary of findings for Key Question 2: medical interventions

Outcome	# of Articles	Overall Strength of Evidence	Comment
Tinnitus-specific quality of life	9 ^{29,30,32,33,35-39}	Insufficient for all interventions	Although most interventions showed no differences relative to placebo, the overall strength of evidence was insufficient because of high risk of bias and inconsistent and imprecise effect estimates. Only single studies evaluated high-frequency electromagnetic energy, ACRN, and acupuncture. Based on single studies for each of these interventions, there is insufficient evidence to conclude whether these findings represent true effects.
Subjective loudness	4 ^{35,36,38,39}	Insufficient for LLLT, ACRN, and acupuncture	Although interventions showed no differences between treatment and placebo groups, the overall strength of evidence was insufficient because of high risk of bias and imprecise effect estimates. Only single studies evaluated high-frequency electromagnetic energy, ACRN, and acupuncture. Based on single studies for each of these interventions, there is insufficient evidence to conclude whether these findings represent true effects.
Sleep disturbance	0	Not applicable	No studies evaluated this outcome.
Anxiety symptoms	1 ³⁶	Insufficient for LLLT	A single study with high risk of bias and small sample size compared laser therapy vs. sham; it showed that laser therapy had greater reduction in anxiety symptoms ($p > 0.05$). The strength of evidence is insufficient to conclude whether these findings represent true effects.
Depression symptoms	1 ³⁶	Insufficient for LLLT	A single study with high risk of bias and small sample size compared laser therapy vs. sham; it showed that laser therapy had greater reduction in depression symptoms ($p > 0.05$). The strength of evidence is insufficient to conclude whether these findings represent true effects.
Global quality of life	0	Not applicable	No studies evaluated this outcome.

Abbreviations: ACRN = acoustic coordinated reset neuromodulation; LLLT = low-level laser therapy

Sound Technology Interventions

Five publications⁴⁰⁻⁴⁴ (of four studies⁴⁰⁻⁴³) evaluated sound technology interventions in head-to-head comparisons (Table D). Interventions included (1) hearing aids versus sound generators;⁴³ (2) Neuromonics with one stage or two stages of stimulus conditions;⁴⁰ (3) information only, information plus relaxation training, information plus long-term low-level white noise (LTWN), and information plus relaxation training plus LTWN;⁴² and (4) cognitive behavioral therapy (CBT) with noise generator (NG), CBT alone, tinnitus education (TE) plus NG, and TE with no NG.⁴¹ Each study assessed a different sound technology. For this reason, formal SOE tables for sound technologies were not included in the review. All of the studies evaluating sound technologies were at high risk of bias and consistency was unknown. Small sample sizes led to these studies being considered imprecise. Overall, there is insufficient information to judge the SOE for the studies evaluating sound technologies.

Adverse effects were not consistently reported or specified in the methods of the studies. None of the studies in the sound technology interventions group reported dropouts related to adverse effects. In general, adverse effects were not mentioned in these reports.

Table D. Summary of findings for Key Question 2: sound technology interventions

Outcome	# of Articles	Overall Strength of Evidence	Comment
Tinnitus-specific quality of life	4 ⁴⁰⁻⁴³	Insufficient	There were no statistically significant differences between treatments in any of the studies, although benefits were reported for hearing aids, sound generators, and Neuromonics. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates.
Subjective loudness	3 ⁴¹⁻⁴³	Insufficient	There were no statistically significant differences between treatments in any of the studies, although benefits were reported for both hearing aids and sound generators. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates.
Sleep disturbance	0	Not applicable	Not applicable.
Anxiety symptoms	1 ⁴¹	Insufficient	All groups in the study demonstrated improvement, but adding a noise generator to tinnitus education or cognitive behavioral therapy did not increase treatment benefits. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates of unknown consistency.
Depression symptoms	1 ⁴¹	Insufficient	A single study with high risk of bias showed no benefit from cognitive behavioral therapy with or without noise generation.
Global quality of life	3 ⁴¹⁻⁴³	Insufficient	Benefit was reported for all interventions involving hearing aids or sound generators, but there were no differences depending on the technology used. ⁴³ No benefits were reported for any other interventions. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates.

Psychological and Behavioral Interventions

A total of 19 RCTs⁴⁵⁻⁶³ evaluated interventions in the psychological and behavioral domain (Table E). Ten^{49,51-53,55-60} RCTs compared some form of CBT with an inactive control, and six^{46,50,54,57-59} compared CBT with another treatment. Two^{48,60} trials compared tinnitus retraining therapy (TRT) with an inactive control, and three^{48,60,61} compared TRT with another treatment. Three^{55,62,63} RCTs compared some form of relaxation therapy with an inactive control, and one⁶³ compared relaxation with another treatment. Six^{45,47,48,55,58,59} studies evaluated some other type of psychological/behavioral therapy compared with an inactive control, and one⁵⁴ involved head-to-head comparisons between treatments.

Adverse effects were not consistently reported or specified in the methods of the studies. None of the studies in the psychological and behavioral interventions group reported dropouts related to adverse effects. Eight studies clearly stated there were no adverse effects reported.^{45-49,52,60,61} One study⁶² reported an increase in negative effects (loudness of and discomfort from their tinnitus) from intensive self-monitoring.

Table E. Summary of findings for Key Question 2: psychological and behavioral interventions

Outcome	# of Articles	Overall Strength of Evidence	Comment
Tinnitus-specific quality of life	19 ⁴⁵⁻⁶³	Low evidence of effect for CBT Insufficient for TRT, relaxation, and other interventions	Benefit for TSQoL is suggested by 6 CBT interventions. However, because of high risk of bias and imprecise effect estimates (i.e., only studies with group sample sizes greater than 20 showed results significantly in favor of treatment compared with inactive controls), confidence is low that these findings lie close to the true effects for this outcome. The strength of evidence is insufficient to conclude whether TRT or relaxation showed improvement in TSQoL because of high risk of bias and imprecise and inconsistent estimates.
Subjective loudness	9 ^{49,51,52,55,56,58,59,62,63}	Low evidence of no effect for CBT Insufficient for relaxation and other interventions	Although 2 interventions had beneficial effects (i.e., CBT + biofeedback, self-help book + telephone therapy), overall consistent evidence suggests that there was no effect for CBT on subjective loudness. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. The strength of evidence is insufficient to conclude whether relaxation showed improvement in subjective loudness because of high risk of bias and imprecise and inconsistent estimates.
Sleep disturbance	5 ^{49,51,56,59,60}	Low evidence of no effect for CBT Insufficient for TRT and yoga	Although treatment benefits were shown for 2 interventions (i.e., CBT + biofeedback, self-help book + telephone therapy), overall, consistent evidence suggests that there was no effect for CBT on sleep disturbance. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. Only single studies with high risk of bias evaluated TRT and yoga.
Anxiety symptoms	5 ^{51,53,56,60,63}	Low evidence of no effect for CBT Insufficient for TRT and relaxation	Although treatment benefits were shown for 1 intervention (self-help book + telephone therapy), overall, consistent evidence suggests that there was no effect for CBT on anxiety symptoms. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. Only single studies with high risk of bias evaluated TRT and relaxation.

Table E. Summary of findings for Key Question 2: psychological and behavioral interventions (continued)

Outcome	# of Articles	Overall Strength of Evidence	Comment
Depression symptoms	11 ^{49,51,53,55-60,62,63}	Low evidence of no effect for CBT Insufficient for TRT and relaxation	Although there are some treatment benefits with various forms of CBT, as well as an intervention involving relaxation and distraction, overall, consistent evidence suggests that there was no effect for CBT on depression symptoms. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. The strength of evidence is insufficient to conclude whether relaxation or TRT showed improvement in depression symptoms because of high risk of bias, imprecise and inconsistent estimates, or only single studies for some interventions in this outcome category.
Global quality of life	6 ^{47,49,52,55,59,60}	Low evidence of no effect for CBT Insufficient for TRT and other interventions	Although there are some treatment benefits for biofeedback-based CBT and bibliotherapy, overall, consistent evidence suggests that there was no effect for CBT on global quality of life. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. Only single studies with high risk of bias evaluated TRT and other interventions.

Abbreviations: CBT = cognitive behavioral therapy; TRT = tinnitus retraining therapy; TSQoL = tinnitus-specific quality of life

KQ3. For adults with subjective idiopathic tinnitus, what prognostic factors, patient characteristics, and/or symptom characteristics affect final treatment outcomes?

No studies were found to address this KQ.

Discussion and Conclusions

In adults with subjective idiopathic (nonpulsatile) tinnitus, the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral interventions (including combinations of interventions) are summarized below (KQ2). This (CER) demonstrates important research gaps with respect to KQ1 (methods to identify those for further evaluation or treatment) and KQ3 (prognostic factors).

When considering the applicability of study findings in general, the study populations were relatively homogeneous and were limited to predominately middle-aged (≥ 50 years of age) persons suffering from subjective idiopathic tinnitus of mild to moderate severity. Of course, hearing loss also increases markedly with age starting in the fourth decade, and hearing loss and tinnitus often co-occur.³ Nevertheless, tinnitus is a problem not only for older adults or for people with clinically significant hearing loss. A recent survey estimated that tinnitus was prevalent in 12.2 percent of the U.S. population under 44 years of age.^{14,64} However, there is little evidence on which to draw conclusions about the efficacy of the therapies in persons younger than 42 years of age. Importantly, there may also be generational differences in the experience of tinnitus based on recent epidemiological research on adults over the age of 45

years.⁴ The finding of generational differences suggests that reports of tinnitus tend to increase with more recent birth cohorts compared with earlier birth cohorts. Researchers should explore age and cohort differences as programs to treat, and possibly even programs to prevent, tinnitus continue to be developed and evaluated.

Tinnitus is a chronic condition. The longest followups in the included studies did not exceed 16 weeks in pharmacological and food supplement studies and 26 weeks in medical interventions. However, followup was extended to 12 months in all of the studies evaluating sound-based treatments^{40,42,43} and even to 18 months for one study.⁴¹ For the psychological and behavioral interventions, many studies evaluated the effectiveness of treatment immediately after treatment, as well as at one or more later followups (up to 18 months⁶⁰). Thus, for the pharmacological and medical intervention categories, the included studies did not provide data on the medium- to long-term effects of the active treatments.

Many of the studies in this review were conducted in Europe, where the professional model of hearing care/audiology is different from that typically seen in the United States. In the United States, the coping/CBT-oriented interventions fall more within the scope of practice of psychologists than audiologists. If future interventions were to require more of this type of psychological intervention, there would need to be a shift in the training of audiologists or a shift to more team-oriented practice involving both audiologists and psychologists.

In general, drawing overall conclusions about treatment benefits proved challenging due to the diversity of interventions and outcomes in the included studies. Studies were heterogeneous in terms of populations, treatments, treatment modalities, study duration and followup periods, and outcome measures. Some interventions showed positive benefits, but it was difficult to judge the degree of clinical significance of the changes observed. Standardized mean differences were estimated for each study because different outcomes were used; the use of diverse outcomes makes it more difficult to assess clinical significance across studies. Even if differences in treatment-placebo scale scores were statistically significant, these differences may not be clinically meaningful. Future research must consider pilot work to establish the validity of many of the outcomes used in the included studies; moreover, specific adaptations of measures validated in nontinnitus populations (e.g., study-specific visual analog scale) should be established in the tinnitus population, particularly for the attributes of change over time. For some of the tinnitus-specific outcomes, it is critical that clinically important differences be established.

Key Findings and Strength of Evidence

Pharmacological or Food Supplement Interventions

A total of 16 unique studies (17 publications)¹²⁻²⁸ evaluated the efficacy of pharmacological interventions or food supplements in tinnitus. The included articles evaluated 14 different interventions, all of which were compared with some form of placebo. For the most part, the interventions failed to demonstrate statistically significant effects compared with placebo on any of the outcomes. Various interventions showed statistically significant effects on some outcomes: nortriptyline¹⁶ and honeybee larvae²⁸ for depression; alprazolam¹⁹ and zinc²⁷ for loudness; and acamprosate²¹ for tinnitus-specific quality of life (TSQoL) measured as “disturbance.” One study¹⁶ found conflicting results for TSQoL (e.g., improved TSQoL or no difference compared with placebo), depending on the instrument used to measure the outcome.

The only intervention that consistently showed statistically significant effects on multiple outcomes was sertraline, which was evaluated against placebo in a 16-week study of 63 persons who had a mean age of 42 years. These persons were recruited from a specialized audiology clinic and given 50 mg/day of the active therapy or placebo. Sertraline was shown to be more efficacious than placebo in reducing loudness, improving global quality of life, and alleviating severity. Sertraline also had a greater impact on reducing depression symptoms, although the reduction failed to reach statistical significance at the 5-percent level on one of the three scales used to measure depression.

Overall, little evidence was found to suggest that the therapies led to improvements over placebo on any of these outcomes. These results are in agreement with the conclusions of previous systematic reviews, which found insufficient, inconsistent, or no evidence of treatment effects.⁶⁵⁻⁷⁰

In terms of SOE, there is insufficient ability to assess whether the published evidence reflects true effects. Effect-size estimates were inconsistent or imprecise, and risk of bias was moderate. Furthermore, most treatments were evaluated in single studies, which may or may not represent the true effect of any particular therapy. Sample sizes tended to be small (<100 persons), and power calculations were largely absent from the published reports, leading to the possibility that many studies were underpowered to detect true effects. Lengths of followup were too short to assess the durability of treatment over time, and the validity and discriminative ability of many outcome measurement instruments was questionable.

Medical Interventions

Eleven studies evaluated four different types of medical interventions that included rTMS,^{29,30,32-34} electromagnetic stimulation,³¹ LLLT,³⁵⁻³⁷ ACRN,³⁹ and acupuncture.³⁸ Almost all studies in this group evaluated TSQoL. In general, SOE for TSQoL is rated as insufficient based on the high risk of bias, and the small sample sizes, lack of power calculations, and lack of specification of the primary outcomes are factors related to the imprecise rating. Many of the studies did not show statistical differences between groups, but limited statistical power is likely an important factor. A clear trend for harms was difficult to specify across the differing interventions. The relative potential for long-term harms could not be evaluated in the short-term treatment trials included in this group.

When considering the individual types of interventions and efficacy with respect to TSQoL, the studies consistently showed no significant difference between treatment and inactive comparators. For rTMS and electromagnetic stimulation, the evidence was rated as insufficient. There was some evidence that longer term effects (improvement in TSQoL scores) occurred with low-frequency rTMS (1 Hz) at up to 6 months followup,²⁹ but this single study had high risk of bias. Our review also showed that adverse effects were generally poorly evaluated and reported. A previous systematic review⁷¹ reached similar conclusions, suggesting that the evidence of benefit for rTMS is limited, and also noted the lack of long-term monitoring within the studies with respect to safety.

With respect to the interventions of ACRN, LLLT, and acupuncture, SOE was rated as insufficient for TSQoL.

Only five trials evaluated the outcome of perceived loudness,^{32,35,36,38,39} and most trials showed no statistical differences between treatment and inactive control groups; however, the studies had small sample sizes and high risk of bias. SOE was rated as insufficient. One intervention (ACRN) showed small differences for one stimulation parameter compared with

sham stimulation.³⁹ However, due to the added problem of the diversity of the medical interventions that evaluated this outcome, we rate the SOE as insufficient for all of these interventions.

A single study examining LLLT relative to sham LLLT evaluated an outcome capturing anxiety symptoms and depression symptoms,³⁶ and was judged to have insufficient SOE. No studies evaluated the effect of these interventions on sleep disturbance and global quality of life.

Future research should provide a more coherent rationale for the particular treatment approaches based on current neurological science principles, including justification for the dose of the intervention.

Sound Technology Interventions

Four unique RCTs⁴⁰⁻⁴³ and a related study⁴⁴ were eligible for this intervention category. Two of the studies^{41,44} evaluated the relative effectiveness of various sound-based interventions to determine whether benefits were enhanced when sound generators were combined with CBT, information, or relaxation therapies. Half of the studies reported some benefits from sound generation, but none demonstrated any statistically significant differences relative to comparator therapies. Two recent systematic reviews that evaluated different sets of eligible studies found similar results. The authors of these reviews discussed the diversity of interventions⁶⁶ in this domain and felt the evidence was insufficient to draw conclusions about the effectiveness of any therapies.^{65,66}

Psychological and Behavioral Interventions

Similar to the medical interventions, the psychological and behavioral interventions were diverse, thereby preventing a clear overall summary of effects. Even the studies with similar interventions had marked differences in the focus and administration of therapy, which enhanced the difficulty of making between-study comparisons. Despite this diversity, the overall SOE was low that CBT and coping approaches showed an improvement in TSQoL, suggesting some confidence that the studies evaluating these interventions reflect true effects.

Behavioral interventions (i.e., relaxation, education, TRT) employed an isolated approach that did not confer the same degree of benefit and were rated as having insufficient SOE, being plagued with the same problems as the studies evaluating pharmacological and medical interventions.

CBT combined with other behavioral interventions were common treatment options. The development of progressive^{72,73} or staged treatments is an active area of interest in the tinnitus field,⁶¹ and this may be a promising avenue for further exploration in future studies. However, trials evaluating complex interventions are problematic if a simple parallel design is employed. Factorial designs will assist in disentangling the relative benefits of the different components of multimodal interventions.

Adverse effects were largely not reported for psychological and behavioral interventions. Some studies reported an absence of adverse effects, but in one study, some patients reported that the self-monitoring of the loudness and discomfort caused by their tinnitus resulted in a worsening of symptoms.

Future Research Recommendations

Key Question 1

- Develop studies to evaluate the comparative effectiveness of instruments used to assess the severity and status of subjective idiopathic tinnitus.

Key Question 2

Population

- Include a broader spectrum of adult patients with respect to age, sex (equal proportion of men), and ethnicity (broader representation of ethnic groups).
- Include patients recruited from primary care settings.
- Capture detailed information about prior treatments and ensure that future studies do not sample only from subjects for whom previous treatments were not effective.
- Specify patient medical histories more clearly.
- Collect information on the use of concomitant interventions.

Comparator and Study Design

- Enroll sufficient samples to show clinically important differences between treatment groups, justify minimum clinically important differences, and justify sample sizes.
- Enroll sample sizes large enough to evaluate confounders.
- Utilize Phase II trials to establish therapeutic doses and preliminary effect sizes to inform the design of Phase III RCTs.
- Have a length of followup that is long enough to study medium- to long-term outcomes.

Intervention

- Explain the dosing rationale for off-label medications.
- Collect information on concomitant medications.
- Specify the training and experience of the person(s) delivering the interventions.

Outcomes

- Identify outcomes as primary or secondary.
- Use scales with established psychometric properties in populations with subjective idiopathic tinnitus to measure patient-reported outcomes.
- Assess the responsiveness to change of outcome measurement instruments (e.g., visual analog scale) in persons with tinnitus.
- Back-translate scales prior to use in languages other than the language in which they were developed.
- Measure global quality of life to capture how persons value the risk-benefit tradeoff between efficacy and adverse effects.
- Use the Consolidated Standards of Reporting Trials (CONSORT)⁷⁴ guidelines for reporting adverse effects (harms).

Other

- Report RCT results in conformity with CONSORT.⁷⁴

- Register study protocols in clinical trial registries and update trial information in these registries regularly.

Key Question 3

- Develop studies to evaluate the natural history and prognostic factors in persons with subjective idiopathic tinnitus.

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Introduction

Background

Tinnitus is not a disease but rather a symptom or condition that can result from a number of underlying causes. In general, tinnitus is the perception of sound in the absence of an external auditory stimulus. The World Health Organization (WHO) describes tinnitus as a “symptom of hearing disorder characterized by the sensation of buzzing, ringing, clicking, pulsations, roaring or other noises in the ear.”¹ Note that in the WHO International Classification of Diseases (ICD), tinnitus is coded as H93.1, which is not a specific ICD-10-CM diagnosis code and cannot be used to indicate a medical diagnosis.¹

Tinnitus can disturb one’s day-to-day life in a number of ways including: causing distress and annoyance, disruption of sleep, anxiety symptoms, and depression symptoms. An estimated 16 percent of the American population (approximately 50 million people) experience tinnitus to some extent, with up to 16 million seeking medical help and 2 million being unable to lead a normal life.² The prevalence of tinnitus increases with age and noise exposure.^{3,4} Similarly, hearing loss also increases with age and noise exposure. Although tinnitus is often associated with hearing loss, tinnitus can affect those who do not have clinically significant hearing loss and not all people who have hearing loss have tinnitus.

A variety of conditions and experiences can lead to tinnitus, but its exact physiology is still unknown. As a symptom, it may be associated with a number of conditions, including various auditory system pathologies, ranging from impacted wax to acoustic tumors, that warrant medical attention. According to the American Tinnitus Association (ATA), noise exposure is the largest attributed cause of tinnitus.⁵ People may acquire tinnitus and hearing loss when they are exposed to hazardous levels of industrial, recreational, or military noise. Tinnitus is the most common service-connected disability among U.S. veterans.² 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. There is growing concern that exposure to recreational noise may result in tinnitus in teenagers and young adults.⁶ Tinnitus can also be a side effect of potentially ototoxic drugs, ranging from aspirin taken to alleviate arthritic pain to aminoglycoside antibiotics and life-saving drugs used to treat cancer.⁷ These effects may be temporary but, especially with respect to aminoglycoside antibiotics and cancer chemotherapeutics, in particular cisplatin, can be permanent.

The severity of tinnitus experienced by patients may vary with, or depend upon, comorbidities. Tinnitus often co-occurs with hearing loss, and the bothersome effects of tinnitus may be alleviated by the use of hearing aids. Individuals who are dual sensory impaired (deaf and blind) may be confused by tinnitus because they do not have visual information to help them understand that their tinnitus is not an external sound. It is common for frequent tinnitus to be associated by mental health conditions, particularly generalized anxiety disorder.⁸⁻¹⁰ Although relatively little is known about tinnitus in younger people compared to what is known about middle-aged and older adults, the connection between tinnitus and mental health issues has been observed in teenagers with hearing loss.¹¹ It is often regarded as a “chronic stressor, creating a vicious circle of stress and exacerbation of tinnitus.”¹²

Classification

In both clinical and academic contexts, there is no consensus on the classification of tinnitus subcategories. A patient is often described as presenting with symptoms of either objective or subjective tinnitus. Objective tinnitus is perceptible by both patient and examiner. Other terms sometimes used for objective tinnitus are “somatosounds” or “somatic tinnitus” or “somatically modulated” tinnitus. Subjective tinnitus is perceptible only by the patient yet is not due to a hallucination. Both forms of tinnitus may or may not be idiopathic. Some investigators have argued that tinnitus should be classified by origin, either as somatic or neurophysiologic.¹³

In this classification by origin, *somatic tinnitus* is categorized as tinnitus with an underlying medical condition that creates internal acoustic mechanical sounds; e.g., the tinnitus has a vascular, muscular, respiratory, or temporomandibular joint (TMJ) origin.¹⁴ The sounds associated with somatic tinnitus (somatosounds) are most commonly pulsatile and may be heard by an observer either directly or through the use of a stethoscope or microphone. Somatic tinnitus requires an examination by a physician ear-specialist (e.g., otolaryngologist) who may be able to identify and treat the underlying condition.¹⁴ Although serious pathology is rarely a cause of tinnitus, pulsatile somatic tinnitus, tinnitus in only one ear (unilateral tinnitus), and tinnitus associated with vertigo require referral to a specialist.¹⁵

In this review, the term *subjective idiopathic tinnitus* will be used rather than neurophysiologic tinnitus because it is the term most commonly used in the current literature. As well, subjective idiopathic tinnitus is the most commonly diagnosed type of tinnitus.¹⁴ It is nonpulsatile, most often bilateral (perceived in both ears), and can only be heard by the patient and not directly observed by a physician, making it difficult to evaluate. Audiological protocols can be used to match the loudness and pitch of the tinnitus perceived by a patient to external sounds with known acoustical parameters.¹⁶ The “phantom sounds” heard by the patient with this type of tinnitus are attributed to a disruption in the neurological auditory pathway. With advances in neuroscience over the last decade, theories have shifted from an emphasis on peripheral to central auditory system involvement. There has also been a shift from conceptualizing tinnitus as a primarily auditory problem to be silenced, to considering it to be a psychological problem with which people can cope.¹⁷⁻¹⁹

Measurement

It is essential to distinguish chronic tinnitus from temporary ear noises that would not be considered pathological (sudden, unilateral, tonal sounds that typically last for up to a minute before decaying). If the patient reports a constant or near-constant perception of tinnitus, the condition is identified as chronic. Typically, chronic tinnitus has a duration of at least 6 months.¹⁴

Various measures can be used to evaluate the presence and severity of the tinnitus.²⁰ There are at least a dozen validated questionnaires for assessing the impact of tinnitus. Psychological grading scales can aid in the discrimination between clinically significant and nonsignificant degrees of tinnitus.²¹

Visual analog scales (VAS) are well known psychometric measures of subjective attitudes and characteristics. With a VAS, patients specify their level of agreement to a statement by indicating a position along a continuous line between two endpoints. The VAS can be used to assess loudness, pitch, and disturbance of the tinnitus.²² Tinnitus questionnaires contain a series of questions and patients select a response to each question from the given choices (usually a

graded scale). Questionnaires, such as the Tinnitus Handicap Inventory (THI) and the Tinnitus Reaction Questionnaire (TRQ), are useful for grading tinnitus severity. However, these and most other tinnitus questionnaires are limited in that they were not designed nor validated to measure the effectiveness of tinnitus interventions.²³ Such effectiveness is referred to as “responsiveness,” which emphasizes effect sizes, content validity, and response scaling that enables detection of change.^{24,25} The Tinnitus Functional Index (TFI) is a self-report questionnaire that has documented validity both for scaling the severity and negative impact of tinnitus and for measuring treatment-related changes in tinnitus. At this time it has not yet been used to evaluate comparative effectiveness of treatments.²⁶

Treatment

Following a medical examination, some patients with subjective idiopathic tinnitus may not receive a recommendation for further treatment, although the practitioner may provide information and assurance of the benign nature of the phenomenon. The complex relationships between tinnitus and a range of physical and mental health conditions have complicated the development and evaluation of intervention strategies. Comorbidities such as hearing loss, mental health problems, or sleep disorders may modulate the experience of tinnitus and direct treatment of those conditions may help to alleviate reactions to tinnitus. For cases of subjective idiopathic tinnitus in which a tinnitus-specific intervention is indicated, there is a wide range of interventions which can include (but are not limited to) pharmacological/food supplements, medical interventions, sound technologies, and psychological/behavioral interventions, as outlined below. These interventions may differ markedly in many dimensions, including the type of expertise required to deliver the treatment, the size and nature of the caseload being treated, and the costs associated with the method of delivery. Some interventions may be offered as programs designed to be cost-effective for large caseloads (e.g., internet CBT), while some may be extremely costly, individualized treatments suitable for only a small number of candidates and requiring a sophisticated technology and a high level of expertise on the part of the practitioner (e.g., cochlear implantation). It is also possible that multiple treatments be provided in combination or in a progressive approach, depending on the needs of the patient.

Pharmacological/Food Supplement Treatments

Pharmacological Treatments

No drug has been approved by the U.S. Food and Drug Administration (FDA) for treating tinnitus. However, various pharmacological treatments, including antidepressants, anxiolytics, vasodilators, and vasoactive substances, and intravenous lidocaine, have been prescribed for tinnitus.²⁷⁻³¹ See Table 1 for examples. For the most part, these treatments have been indirect solutions because they focus on tinnitus-associated symptoms, such as depression symptoms, stress, or sleep disturbance.³² However, newer medications that attempt to modulate the central auditory pathways, such as pramipexole, are being investigated and may have promise for reducing the perception of tinnitus.³³

Table 1. Some pharmacological treatments for tinnitus

Drug Class	Agents (Examples)
Antidepressants	Tricyclics: amitriptyline, nortriptyline, trimipramine Selective serotonin-reuptake inhibitors (SSRI): fluoxetine, paroxetine Other: trazodone
Anxiolytics	Alprazolam
Vasodilators/Vasoactive Substances	Prostaglandin E1
Other	Lidocaine, gabapentin, Botox [®] , pramipexole

Abbreviations: Botox = botulinum toxin type A; SSRI = selective serotonin-reuptake inhibitors

Food Supplements

Food supplements, such as Gingko biloba extracts, are also being used by patients with tinnitus. Extracts from Gingko biloba leaves are a traditional Chinese medicinal treatment used to increase blood flow, inhibit the platelet-activating factor, alter neuron metabolism, and prevent free radicals from damaging cell membranes. These improvements, as well as relief from tinnitus, are claimed by some to be attributed to the chemical compounds flavonoid and terpenoid, which are found within the Gingko biloba plant.³⁴

Medical Interventions

Low Level Laser Treatments

Low level laser therapy (LLLT) 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.

Temporomandibular Joint Treatment

Tinnitus, vertigo, and otalgia are symptoms that have been linked to temporomandibular joint (TMJ) disease.³⁶ This disease consists of a collection of medical and dental conditions that affect the TMJ, masticatory muscles, and/or the adjoining structures, causing pain and tenderness, most frequently felt in the jaw and the temple but also in the ear and surrounding area.³⁷ Treatment can range from the use of dental orthotics and self-care instructions to surgery (in instances where injury to the jaw is the underlying cause).³⁸

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) delivers an electro-magnetic field to the superficial cerebral cortices modulating the excitability in the area of the cerebral cortex believed to be associated with tinnitus.³⁹ It has been shown to provide tinnitus relief in some cases, however, the underlying mechanisms of this effect are not yet understood, and no commercial treatment using this technique is currently available.⁴⁰

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy was reported to aid in the relief of tinnitus associated with sudden sensorineural hearing loss by improving the oxygen supply to the inner ear.⁴¹ This therapy, which is used to treat a variety of medical conditions, requires that the patient sit inside a

pressured chamber containing an atmosphere of 100 percent oxygen, which increases the oxygen supply to body tissues.

Dietary Modifications

Limiting the intake of high-sodium foods, caffeine, chocolate, and other stimulants and avoiding refined sugars, artificial sweeteners, saturated and unsaturated fats, and monosodium glutamate are examples of diet modifications.⁴²⁻⁴⁴ This is not a comprehensive list.

Complementary and Alternative Medicine Therapies

Individuals seeking general information about tinnitus relief on the Internet will find a large array of complementary and alternative medicine (CAM) approaches proposed to relieve and even “cure” tinnitus. Numerous therapies that are considered CAM include, but are not limited to, the use of supplements or herbal remedies (e.g., ginkgo biloba, feverfew), mind and body approaches (e.g., meditation), manipulative and body-based practices (e.g., spinal manipulation, massage), whole body approaches (e.g., Traditional Chinese medicine, Aryurveda) and other non-allopathic therapies.⁴⁵

Sound Technologies

Hearing Aids, Cochlear Implants, Maskers and Sound Generators

Hearing aids are one option for reducing reactions to tinnitus if the person also has hearing loss. Hearing aids can increase the overall level of ambient sound delivered to the patient, which can accomplish the objectives normally targeted for sound therapy. Some hearing aids have sound generators built in, which can be added to the amplified ambient sound. These devices are referred to as ‘combination instruments’ and are often considered as an option for patients who have hearing loss and bothersome tinnitus.⁴⁶

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 until recently they were considered to be appropriate for use by only a very specific subset of patients (e.g., people who have bilateral profound sensorineural hearing loss).⁴⁰ Very recently, cochlear implants have also been used successfully to reduce tinnitus in subjects with single-sided deafness, although this may be considered to be ‘off label’ use.⁴⁷⁻⁴⁹

Tinnitus masking was developed in the 1970s. The original purpose was to present a sufficiently intense signal matched to the characteristics of the individual’s tinnitus perception (e.g., frequency of tone, bandwidth of noise) that would cover up, or “mask,” the patient’s tinnitus. Currently, the purpose is to use sound to achieve a sense of relief from the stress or tension caused by tinnitus.⁵⁰ This is done by using ear-level sound generators, which may be called “maskers,” that generate wideband noise. The word “masking” has created confusion—the method is now thought of as “sound-based relief.” Sound generators are also available as stationary tabletop devices. Sound generators (masking devices) have received Class II approval from the FDA. However, because they are considered to be “experimental, investigational, or unproven” therapies,⁵⁰ they are generally not covered under health insurance plans.⁵¹

Neuromonics Tinnitus Treatment

Neuromonics Tinnitus Treatment is a combination of acoustic stimulation with a structured program of counseling and support by a clinician trained specifically in tinnitus rehabilitation.⁵²

The acoustic component of the treatment is designed to provide “stimulation to auditory pathways deprived by hearing loss, engage positively with the limbic system, and allow intermittent, momentary tinnitus perception within a pleasant and relaxing stimulus, thereby facilitating desensitization to the tinnitus signal.”⁵³ The device with headphones (likened to an MP3 player in appearance) delivers musical sound customized to the hearing loss of the individual. The typical treatment program lasts 6 months.

Psychological/Behavioral Treatments

In addition to its association with many physical health problems, tinnitus is also associated with many clinical and subclinical psychological health problems, both as a cause and consequence of tinnitus. For example, individuals with tinnitus may experience difficulties with attention and anxiety symptoms and those who are most distressed by tinnitus may be psychologically vulnerable.⁵⁴ Treatments in this category enlist the use of psychological and/or behavioral interventions to reduce the negative consequences of tinnitus.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) may effectively increase quality of life and the patient’s ability to deal with chronic tinnitus by restructuring thought patterns and habituating those patterns when the patient is reacting to tinnitus.⁵⁵ It is suggested as one of the first recommendations a general practitioner should make according to the good-practice guidelines developed by the Department of Health in the United Kingdom.⁵⁶ CBT encompasses a number of possible therapeutic procedures, including cognitive and/or behavioral techniques.⁵⁷ Importantly, these interventions apply principles of learning and/or cognitive theories of affect, regulation, and behavior change.⁵⁸ The overall goal is to change the psychological processes that are assumed to maintain or exacerbate the distress associated with tinnitus.

Tinnitus Retraining Therapy

Since its proposal in 1990, tinnitus retraining therapy (TRT) has been used to reprogram how a patient interprets the “tinnitus” sounds by combining sound therapy with directive counseling.⁵⁹ A key feature of TRT is that sound is used, but for a different purpose than for masking. With TRT, sound is not intended to induce a sense of relief, but rather to create a background of sound to make the tinnitus less noticeable. TRT also involves fairly extensive counseling, which is based on the “neurophysiological model.”⁶⁰ This model is used to help patients understand that tinnitus is a meaningless signal. The combination of sound therapy and counseling with TRT is designed to lead to habituation, such that the patient does not normally pay attention to the tinnitus and does not react to it when it does come into consciousness.^{59,60} Since TRT depends on both the use of sound and counseling, it spans two main categories of Psychological/Behavioral or Sound Technologies interventions. 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. TRT is most often compared to other treatments situated in the Psychological/Behavioral category rather than being compared to other technologies. However, one study⁶¹ involving TRT was placed in the Sound Technology category because it did involve a comparison between two technologies, sound generators and hearing aids, both used with TRT (i.e., the comparison did not pit TRT against an inactive control or another intervention that differed in terms of TRT itself). Also note that other interventions categorized as Psychological/Behavioral do not preclude the use of sound

technology; for example 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.

Biofeedback, Education, and Relaxation Therapies

Biofeedback, education, and relaxation therapies aim to teach the patient to control or habituate to the perceived ringing and the subsequent distress. Biofeedback treatments are based on the presumption that the stress caused by tinnitus exaggerates a patient's discomfort and that the patient can learn to control stress using biofeedback to monitor it. Biofeedback therapy for tinnitus involves listening to an audio signal produced by electromyography (EMG) of the frontalis muscle. EMG uses surface electrodes in the detection of muscle action potentials from underlying skeletal muscles that initiate muscle contractions.¹⁹

Educating patients about their tinnitus has been proposed to improve the management of tinnitus-related symptoms and the associated discomfort.¹⁹ It is especially important that patients are taught strategies to self-manage their tinnitus. No method currently exists to reduce or eliminate the sensation of tinnitus, thus patients need to learn how to help themselves for a potential lifetime of tinnitus management.¹³

Relaxation therapies also offer strategies to focus the patient's attention away from the sound, aiming to psychologically alleviate stress responses to tinnitus.⁶² Although these therapies may not eliminate the tinnitus, they aim to improve quality of life through habituation to decrease consciousness of the noise. Relaxation therapies to address emotional responses to tinnitus are often combined with CBT.

Progressive Tinnitus Management

Progressive tinnitus management (PTM) is a methodology developed by the Veterans Health Administration (VHA). The VHA has endorsed PTM as the standard method of treatment at their medical centers.⁴⁶ PTM uses elements of hearing aids, masking, TRT, and CBT. PTM is a stepped-care approach, based on education leading to self-efficacy, and it creates a framework for management that is flexible to accommodate differing requirements of clinicians and patients.^{46,63} A similar progressive stage treatment approach has recently been developed by others.⁶⁴

Scope and Key Questions

In a rehabilitative context, those with tinnitus are more likely than those without tinnitus to seek professional help and accept hearing aids, presumably because the combination of tinnitus and hearing loss increases disability,^{4,65} yet typical audiological interventions focus on the remediation of hearing loss rather than on treatments for tinnitus.⁴ Recent research findings from cognitive and auditory neuroscience studies have advanced knowledge of the biological underpinnings of some forms of tinnitus, while findings from clinical psychological studies have underscored the interactions among the auditory, cognitive, affective, and mental health issues that must be considered when designing and evaluating interventions to meet the needs of clinical subpopulations of patients. How some people "live with it" so much better than others is still not clear. Despite many available and promising treatments, there are no universally accepted therapies for managing tinnitus.

In 2008, the Tinnitus Research Initiative (TRI) created, and still continues to modify, a flowchart outlining steps for the diagnosis and management of tinnitus; however, this clinical

protocol has yet to be adopted by any government or agency because the evidentiary base has not yet been evaluated.⁶⁶ The usability of the TRI flowchart is limited as it reflects a biomedical approach: an approach that would be used by medical physicians, but not by providers such as audiologists or psychologists who implement behavioral methods. Organizations such as the ATA provide information on a variety of treatment options, but do not endorse or recommend any specific treatment. In 2009, the Department of Health in the United Kingdom issued the “Provision of Services for Adults with Tinnitus: A Good Practice Guide”⁵⁶ for the commissioning of tinnitus services and for managing tinnitus from primary care onwards.⁶⁷ The TRI flowchart and the United Kingdom Good Practice Guide reflect current best practices recommendations. Guidelines are currently not standardized in the United States, although the efforts and strategies of individual researchers appear in the research literature.^{14,68}

As there is no “cure” for tinnitus, the absence of firm guidelines and management strategies demonstrates the need for further evaluation of current treatment options. This review aims to explore prognostic factors and strategies for the optimal management of tinnitus and to clarify the effectiveness of the various tinnitus treatments currently in use and their measurable outcomes. It also identifies gaps in the existing literature that will inform directions for future research.

Key Questions and Eligibility Criteria

We identify the eligibility criteria for each Key Question (KQ) by describing inclusion and exclusion criteria for the population, intervention, comparators, outcomes, timing and setting (PICOTS).

KQ1. In patients with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds, etc.) what is the comparative effectiveness of methods used to identify patients for further evaluation or treatment?

Population(s)

Adult patients (18 and over) presenting with symptoms of tinnitus.

Interventions

Direct observation or observation of sound with stethoscope; referral to a health professional with expertise on managing tinnitus (e.g., otolaryngologist, audiologist, neurologist, mental health professional); administration of scales/or questionnaires to assess severity (e.g., THI, TRQ, TFI, VAS).

Comparators

Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus.

Outcomes

Final outcome: (1) No treatment; (2) need for specialized treatment (e.g., audiology, otolaryngology, neurology, mental health care); (3) extent of intervention.

Timing or Followup

No restrictions.

Setting

Primary care; specialty care (audiology, otolaryngology, neurology, mental health care).

Note: For KQ2 and KQ3, adults diagnosed with unilateral and/or pulsatile tinnitus need to be evaluated for other medical conditions, such as acoustic neuromas. This review will include only those cases in which a medically serious underlying pathology as the source of the tinnitus has already been ruled out.

KQ2. In adults with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral interventions, including combinations of interventions?

Population(s)

Adult patients (18 and over) with a diagnosis of subjective idiopathic (nonpulsatile) tinnitus who are sufficiently bothered by tinnitus that they seek a treatment intervention.

Interventions

Any treatment/therapy used to reduce/help cope with tinnitus including but not limited to the following:

Pharmacological and Food Supplement Interventions

- Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, trimipramine)
- Selective serotonin-reuptake inhibitors: fluoxetine and paroxetine
- Other: trazodone; anxiolytics (e.g., alprazolam); vasodilators and vasoactive substances (e.g., prostaglandin E1); intravenous lidocaine; gabapentin; Botox (botulinum toxin type A); and pramipexole
- Complementary and alternative medicine (CAM) therapies: Gingko biloba extracts; food supplements)

Medical Interventions

- Low level laser treatments (LLLT)
- TMJ treatment: dental orthotics and self-care; surgery
- Transcranial magnetic stimulation (TMS)
- Hyperbaric oxygen therapy
- Dietary modifications
- Complementary and alternative medicine (CAM) therapies that are not food supplements; acupuncture; diet, lifestyle, and sleep modifications (e.g., caffeine avoidance, exercise)
- Other related interventions that require administration by a clinician

Sound Treatments/Technologies Interventions

- Hearing aids
- Cochlear implants
- Sound generators/maskers (both wearable and stationary)
- Neuromonics

Psychological/Behavioral Interventions

- Cognitive behavioral therapy (CBT), coping training, psychotherapy
- Tinnitus retraining therapy (TRT)
- Biofeedback
- Education
- Relaxation therapies
- Progressive tinnitus management (PTM)

Combination Therapies

- Any combination of tinnitus interventions (e.g., pharmacological treatment with CBT)

Comparators

Inactive controls (including placebo; no treatment; wait list; sham interventions).

Active controls (including treatment as usual; other intervention/treatments).

Outcomes

Included Outcomes of Benefit

1. Tinnitus-specific Quality of Life
2. Sleep disturbance
3. Anxiety symptoms
4. Depression symptoms
5. Subjective loudness
6. Global Quality of Life

Included Adverse Effects

1. Worsening of tinnitus
2. Sedation
3. Surgical complications
4. All other treatment-emergent adverse effects reported for the various interventions

Excluded

Studies that reported outcomes on a non-numeric scale, such as loudness in decibels (dBs).

No other outcomes were used to exclude studies.

Timing or Followup

No restrictions.

Setting

Primary care; specialty care (audiology, otolaryngology, neurology, and mental health care).

Setting was not used as an exclusion criterion.

KQ3. For adults with subjective idiopathic tinnitus, what prognostic factors, patient characteristics, and/or symptom characteristics affect final treatment outcomes?

Population(s)

Adults (18 and over) with a diagnosis of subjective idiopathic tinnitus sufficiently bothered by tinnitus that they are seeking a treatment intervention.

Interventions

Any treatment/therapy used to reduce/help/cope with tinnitus including, but not limited to, those described in KQ2.

Comparators

- Prognostic factors: length of time to treatment after onset, audiological factors (degree and type of hearing loss, hyperacusis, loudness tolerance, masking criteria, etc.), head injury, anxiety symptoms, mental health disorders, and duration of tinnitus
- Patient characteristics: age, sex, race, medical or mental health comorbidities, socioeconomic factors, noise exposure (environmental, recreational and work-related (including active and past military duty, and occupational hazards)), involvement in litigation, third-party coverage
- Symptom characteristics: origin/presumed etiology of tinnitus, tinnitus duration since onset, subcategory of tinnitus, severity of tinnitus

Outcomes

Final Outcomes

1. Time until improvement
2. Sleep disturbance
3. Tinnitus-specific Quality of Life
4. Anxiety symptoms
5. Depression symptoms
6. Subjective loudness
7. Global Quality of Life
8. Return to “normal” work

Adverse Effects

1. Worsening of tinnitus
2. Sedation
3. Surgical complications
4. Any other treatment-emergent adverse effects.

Timing or Followup

No restrictions.

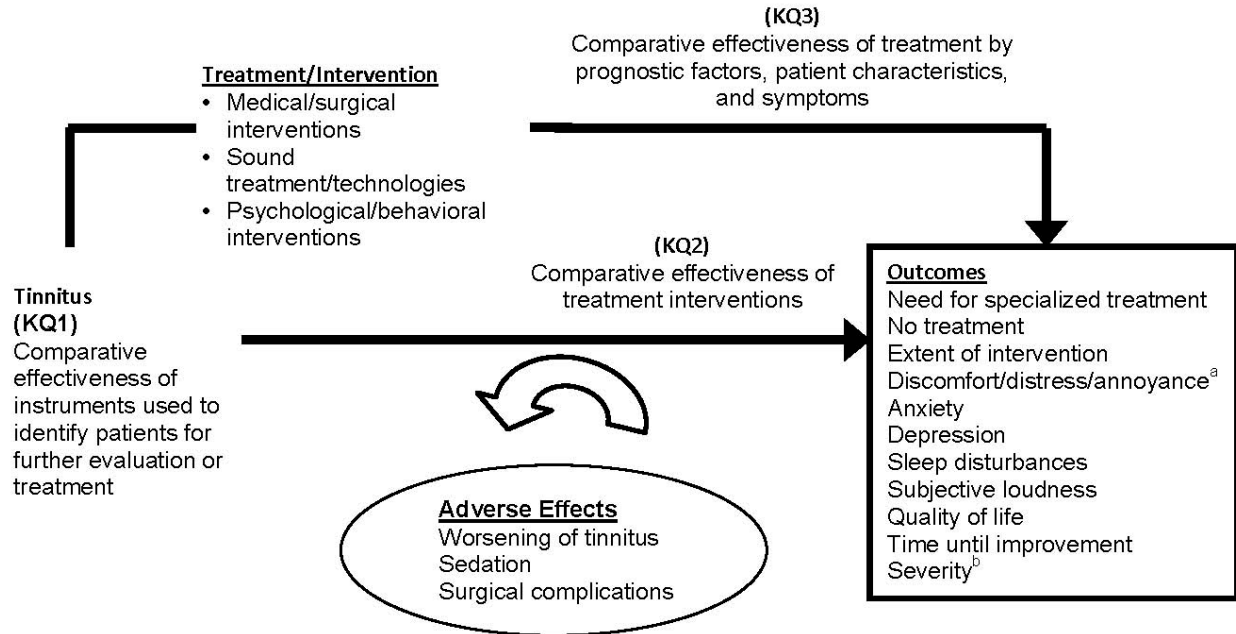
Setting

Primary care; specialty care (audiology, otolaryngology, neurology, mental health).

Analytic Framework

Following consultation with key informants, the Agency for Healthcare Research and Quality (AHRQ) Task Order Officer (TOO), and the investigative team, key research questions were developed. Figure 1 shows a flow diagram indicating the relationship between research questions in this Comparative Effectiveness Review (CER). This framework depicts the KQ as outlined in the PICOTS format (Population(s), Interventions, Comparators, Outcomes, Timing or followup, and Setting). The PICOTS components for each KQ are provided in full detail in Table 2.

Figure 1. Analytic framework



*Any studies that used the terms “annoyance” or “distress” to describe their outcomes were included under the category of “discomfort.”

**The outcome “severity” was added during data extraction. As severity was an outcome reported in 18 of 34 papers, it was decided that it should not be collapsed into any other outcome category.

Methods

Topic Refinement

The topic of this report and preliminary Key Questions (KQs) were developed through a process involving the public, the Scientific Resource Center for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ), and various stakeholder groups. The KQs developed as a result of this process were posted on AHRQ's website for public comment in October 2012 for 4 weeks and revised as needed. Study, patient, intervention, eligibility criteria, and outcomes, were refined and agreed upon through discussions between the McMaster University Evidence-based Practice Center (EPC), the Technical Expert Panel (TEP) members, the AHRQ Task Order Officer (TOO), and comments received from the public posting of the Key Questions. (www.effectivehealthcare.ahrq.gov/ehc/products/371/811/Tinnitus_Protocol_20120222.pdf).

The EPC convened a group of experts in the fields of Tinnitus and systematic review methods to form the TEP. Members of the TEP provided input to help interpret the KQs guiding this review, identify important issues, and define parameters for the review of evidence.

Search Strategy

The search was conducted in six databases: MEDLINE[®], EMBASE[®], Cochrane Central, PsycINFO[®], AMED[®], and CINAHL[®]. These databases were chosen because they represent the best sources for a broad range of high-quality literature relevant to this topic. In particular, Embase[®] seems to index a wider range of audiology journals than MEDLINE[®], including *Audiological Medicine*. AMED[®] and CINAHL[®] have been included because of the inclusion of complementary and alternative medicine therapies in the interventions considered in this review.

Tinnitus is well indexed in the medical bibliographic databases, and there were few alternative terms that needed to be included in the search strategy. The search strategy used combinations of controlled vocabulary (medical subject headings (MeSH[®]), keywords) and text words. The search was restricted to human-focused studies (specifically removing those results that only include animal data), and certain citation types not included in this review were removed as part of the search (see Appendix A for detailed search strategy by database). The databases were searched from January 1970 to June 2012. The basic search strategy is listed below.

1. Tinnitus/or tinnitus.ti.
2. animals/not humans/
3. 1 not 2
4. limit 3 to English language
5. limit 4 to (case reports or comment or editorial or in vitro or interview or letter or newspaper article or webcasts)
6. 4 not 5

Citations meeting this search criteria were downloaded into Reference Manager[®] 12 (Thomson Reuters, New York, NY) and then imported into a systematic review software program, DistillerSR (Evidence Partners Inc., Ottawa, Canada), for screening. Once in DistillerSR, citations were screened in duplicate by trained members of the synthesis team using the specified eligibility criteria for the review. Articles marked for inclusion by either team

member proceeded to full text rating, which was also completed independently by two reviewers. All disagreements were resolved through discussions with the synthesis team, and inclusion results were reviewed by a third person.

In addition to the electronic database search, review of reference lists of eligible studies at full text screening was undertaken. Systematic reviews and meta-analyses were separately coded for retrieval during screening, and the reference lists were reviewed. Any potentially relevant citations were cross-checked within the citation database. Any references not found within the database were retrieved, added, and screened at full text.

Grey Literature

Three types of grey literature sources were searched: regulatory agency Web sites, clinical trial databases, and conference sources. The regulatory information included the U.S Food and Drug Administration (FDA), Health Canada, and the European Medicines Agency. The clinical trial databases searched include: clinicaltrials.gov, clinicaltrialsregister.eu, metaRegister of Current Controlled Trials, Clinical Trial Registries, Clinical Study Results, and World Health Organization Clinical Trials. Conference papers were searched in the Conference Papers Index for the last 2 years only. This was to allow for the inclusion of studies that have been presented at conferences but have not yet had the chance to be published.

In addition, the Web sites of the following tinnitus-related organizations were searched for additional citations:

- The American Tinnitus Association
- The Association for Research in Otolaryngology
- American Academy of Audiology
- Emory University Tinnitus and Hyperacusis Center
- Tinnitus Research Initiative
- Deafness Research (United Kingdom)

The Scientific Resource Center also requested the Scientific Information Packages for drugs and devices and any missing relevant studies were added to the screening process.

Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are based on the eligibility criteria from the PICOTS identified in Chapter 1, and are summarized below in Table 2. Based on input from the TEP indicating that the majority of available studies would be published in English-language journals, non-English-language publications were excluded.^{69,70} Included studies were randomized controlled trials (RCTs) or observational studies (e.g., cohort, case-control) with true control groups and provided sufficient detail about methods and results to enable use and aggregation of the data and results. Meta-analyses and systematic and narrative reviews were excluded, but reference lists were evaluated for potentially relevant citations. Case reports, case series, editorials, comments, letters, opinion pieces, conference proceedings and abstracts, books, and book chapters were excluded.

At the full text screening level, articles were excluded for any of the previously cited reasons. They were also excluded for KQ2 and KQ3 if there was not a treatment intervention for tinnitus (e.g., prevalence studies, studies to determine effects of tinnitus on brain wave patterns or memory); if tinnitus was somatic (e.g., the result of middle ear pathologies or ototoxicity, or was

pulsatile in nature), or the intervention was a stapedectomy or tympanoplasty; and/or certain study designs/methods of presenting data (e.g., only determined various effects, a nonrandomized head-to-head design, or did not give sufficient detail of data for analyses).

Refer to Appendix B for Screening and Data Extraction Forms and the accompanying help sheets.

Table 2. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	<p>KQ1: Adult (≥ 18 yrs) patients who visit healthcare practitioners with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds)</p> <p>KQ2 & 3: Adults (≥ 18 yrs) with a diagnosis of subjective idiopathic (nonpulsatile) tinnitus who are sufficiently bothered by tinnitus that they are seeking a treatment intervention</p>	<ul style="list-style-type: none"> • Subjects < 18 years of age • Dx of pulsatile tinnitus • Unilateral cases with specific medical Dx (e.g., paraganglioma, acoustic neuroma) • Tinnitus as side effect of drugs • Nonhuman subjects
Interventions	<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, TSI, VAS)</p> <p>KQ2: Any treatment/therapy used to reduce/help cope with tinnitus including but not limited to:</p> <p>Pharmacological</p> <ul style="list-style-type: none"> • Pharmacological treatments: Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, trimipramine); selective serotonin-reuptake inhibitors (e.g., fluoxetine, paroxetine); other: trazodone, anxiolytics (e.g., alprazolam), vasodilators and vasoactive substances (e.g., prostaglandin E1), intravenous lidocaine; gabapentin, Botox (botulinum toxin type A), and pramipexole, Complementary and alternative medicine therapies: Gingko biloba extracts or other food supplements <p>Medical</p> <ul style="list-style-type: none"> • LLLT • TMJ treatment: dental orthotics and self-care; surgery • Transcranial magnetic stimulation • Hyperbaric oxygen therapy • Complementary and alternative medicine therapies: acupuncture; diet, lifestyle, and sleep modifications (e.g., caffeine avoidance, exercise) <p>Sound Treatments/Technologies</p> <ul style="list-style-type: none"> • Hearing aids, cochlear implants, sound generators, maskers • Neuromonics <p>Psychological/Behavioral</p> <ul style="list-style-type: none"> • CBT, biofeedback, education, relaxation therapies, PTM, TRT <p>Combination Therapies</p> <ul style="list-style-type: none"> • Any combination of tinnitus interventions (e.g., pharmacological treatment with DBT) <p>KQ3: Any treatment/therapy used to reduce/help/cope with tinnitus including but not limited to those described in KQ2</p>	<p>KQ1: Nondirect observations</p> <p>KQ2: No exclusions for interventions</p> <p>KQ3: No exclusions for interventions</p>

Table 2. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Comparators	<p>KQ1: Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus</p> <p>KQ2:</p> <ul style="list-style-type: none"> • Inactive controls (including placebo; no treatment; wait list; sham interventions) • Active controls (including treatment as usual; other intervention/treatments) <p>KQ3:</p> <ul style="list-style-type: none"> • Prognostic factors: length of time to treatment after onset, audiological factors (e.g., degree and type of hearing loss, hyperacusis, loudness tolerance, masking criteria), head injury, anxiety symptoms, mental health disorders, and duration of tinnitus. • Patient characteristics: age, sex, race, medical or mental health comorbidities, socioeconomic factors, noise exposure (environmental, recreational, work-related (including active and past military duty, and occupational hazards)), involvement in litigation, third-party coverage <p>Symptom characteristics: origin/presumed etiology of tinnitus, tinnitus duration since onset, subcategory of tinnitus, severity of tinnitus</p>	<p>KQ1: No exclusions</p> <p>KQ2: No exclusions</p> <p>KQ3: No exclusions</p>
Comparators	<p>KQ1: Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus</p> <p>KQ2:</p> <ul style="list-style-type: none"> • Inactive controls (including placebo; no treatment; wait list; sham interventions) • Active controls (including treatment as usual; other intervention/treatments) <p>KQ3:</p> <ul style="list-style-type: none"> • Prognostic factors: length of time to treatment after onset, audiological factors (e.g., degree and type of hearing loss, hyperacusis, loudness tolerance, masking criteria), head injury, anxiety symptoms, mental health disorders, and duration of tinnitus. • Patient characteristics: age, sex, race, medical or mental health comorbidities, socioeconomic factors, noise exposure (environmental, recreational, work-related (including active and past military duty, and occupational hazards)), involvement in litigation, third-party coverage • Symptom characteristics: origin/presumed etiology of tinnitus, tinnitus duration since onset, subcategory of tinnitus, severity of tinnitus 	<p>KQ1: No exclusions</p> <p>KQ2: No exclusions</p> <p>KQ3: No exclusions</p>
Outcomes	<p>KQ1: Final outcome: No treatment; need for specialized treatment (e.g., audiology, otolaryngology, neurology, mental health care); extent of intervention</p> <p>KQ2: Tinnitus-specific Quality of Life, Sleep disturbance, depression symptoms, subjective loudness, Global quality of life, tinnitus severity, adverse effects (worsening of tinnitus, sedation, surgical complications, other treatment emergent events)</p> <p>KQ3: Time until improvement, sleep disturbance, discomfort, anxiety symptom, depression symptoms, subjective loudness, quality of life, return to “normal” work, adverse effects (worsening of tinnitus, sedation, surgical complications)</p>	<p>Studies where outcomes were reported on non-numeric scales (such as loudness in dB).</p>
Publication languages	English	Non-English

Table 2. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Study design	<p>All KQs:</p> <ul style="list-style-type: none"> • RCTs or non-randomized (quasi-randomized, controlled clinical studies) with at least one comparator group • Original research studies must provide sufficient detail about methods and results to enable use and aggregation of the data and results • Relevant outcomes must be able to be extracted from data in the papers • Controlled experimental studies (manipulation of treatment) 	<p>All KQs:</p> <p>Studies where:</p> <ul style="list-style-type: none"> • Only scatter plots and bar graphs (no numerical data) presented • Effect size could not be estimated (i.e., only p values reported with no outcome measure data) • Outcome results reported results in the form of improvement (percent) or responder versus non-responder • If the studies did not state a priori that the results would be reported in this way <p>KQ2:</p> <ul style="list-style-type: none"> • Cross-over studies that did not report first period data • Observational studies without comparators (case reports, case series, before-after studies) • Observational studies without interventions (case-control studies, population cohort studies) • Systematic reviews and narrative reviews (evaluated for reference list review) • Editorials, comments, letters, opinion pieces, and abstracts
Setting	Primary care; specialty care (audiology, otolaryngology, neurology, mental health)	No exclusions
Other criteria	<p>Studies must address one or more of the following for tinnitus:</p> <p>KQ1: Instruments used to identify patients for further evaluation or treatment</p> <p>KQ2: Treatment modality</p> <p>KQ3: Predictors of treatment outcomes (prognostic factors, patient characteristics, and symptom characteristics)</p>	

Abbreviations: DBT = cognitive behavioral therapy; dB = decibals; Dx = diagnosis; KQ = Key Question; LLLT = low level laser LL treatment; PTM = progressive tinnitus management; RCT = randomized controlled trial; THI = Tinnitus Handicap Inventory; TMJ = temporomandibular joint; TRQ = Tinnitus Reaction Questionnaire; TRT = tinnitus retraining therapy; TSI = Tinnitus Severity Index; VAS = visual analogue scale; yrs = years

Data Extraction

The Evidence-based Practice Center staff members and clinical experts conducting this review jointly developed the evidence table that was used to abstract data from the studies (Appendix B). The table was designed to provide enough information to enable readers to understand the studies, including types of study design, descriptions of the study populations (for applicability), description of the intervention, appropriateness of comparison groups, validated questionnaire measures used, baseline and outcome data on constructs of interest, and followup conducted. Details of the patient population extracted included age, sex, duration of tinnitus,

severity of tinnitus, audiological factors, and comorbidities. Data were also collected about the site where study participants were recruited and the professional setting (primary care, audiology, otolaryngology, neurology, or mental health). In addition to outcomes related to treatment effectiveness, all available data on harms or adverse effects of treatments were extracted.

To ensure quality control, the team extracted several articles into the evidence table and then reconvened as a group to discuss the utility of the table design. This process was repeated until it was decided that the table included the appropriate categories to gather the information contained in the articles. All team members shared the task of initially entering information into the evidence table. Another team member then reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The full research team met regularly during the article abstraction period to discuss any conflicts or issues related to the data abstraction process.

Assessment of Methodological Risk of Bias of Individual Studies

To assess individual study quality, methods recommended by AHRQ for its EPC Program in Chapter 5 of the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (hereafter Methods Guide) were employed.⁷¹ Two raters assessed the quality of individual studies using standardized quality assessment tools. Inconsistency among raters was minimized by providing standardized instructions and clear decision rules. Disagreement between raters was resolved by consensus.

Risk of bias assessment tools consist of five domains: population, outcome, exposure, statistical analysis, and, for RCTs, randomization, blinding, and withdrawals. These domains were adapted from the Newcastle-Ottawa quality assessment scales for case-control studies and cohort studies⁷² and the Jadad scale for RCTs.⁷³ Additional items were needed for the Newcastle Ottawa Scale (NOS) to describe the population for cohort studies (2 items) and three additional items for the Jadad scale. Each quality item was scored as yes, no, or unsure. An answer of “no” corresponds to a high risk of bias, “unsure” corresponds to a possible or unclear risk of bias, and “yes” corresponds to a low risk of bias. For each quality item, the responses were graphed and problem areas discussed. An overall quality score was not calculated.

Assessing Applicability

Applicability may be affected by differences between what occurs in research and what happens in everyday clinical practice. Applicability was assessed in accordance with AHRQ standards.⁷⁴ The basis for applicability assessment of findings was limited to the populations, interventions, outcomes, and settings described in the protocol and the PICOTS. Comorbidities, age of subjects, location where study subjects were recruited, specific treatment provider, and length of time to treatment are examples of a priori factors that may limit applicability. Subgroup factors that may cause or explain heterogeneity of treatment effect may include patients provided with proper audiological care before tinnitus treatment, psychological and hearing loss comorbidities, and subtyping by prognostic, patient, and symptom characteristics that may interact with treatment outcome.

Data Synthesis

Qualitative Synthesis

Study results are presented in three sections based on the three KQs. All included studies have been summarized in narrative form, and summary tables have been created showing key study characteristics, methodological limitations, and any other important aspect related to each Key Question.

Quantitative Synthesis

The outcomes of interest in each study were reported using different outcome measures on a continuous scale. With the intention to perform meta-analysis using continuous data, immediate post-treatment data (mean, standard deviation, and sample size) for each treatment group were utilized. The DerSimonian and Laird random effects models with inverse variance method were selected to generate the summary measures of effect in the form of standardized mean difference (SMD) for each outcome. The SMD was selected as a summary statistic because the studies in this systematic review often assessed the same outcome domains using a variety of measures and scales. In this situation, it was necessary to standardize the results of the studies before they could be compared across studies or combined in a quantitative synthesis. SMD was calculated using change from baseline data, (i.e., mean difference between pre-treatment (baseline) and post-treatment (final/endpoint) scores, along with its standard deviation for both intervention and control groups). In studies where change from baseline data was not reported for treatment groups, the mean difference was calculated from pre- and post-treatment scores provided and standard deviation was computed using the following equation:

$$SD_{Change} = \sqrt{SD_{Baseline}^2 + SD_{Final}^2 - (2 \times Corr \times SD_{Baseline} \times SD_{Final})}$$

Where, SD_{change} = Standard deviation of mean difference (pre and post treatment),
 $SD_{Baseline}$ = Standard deviation if pre-treatment score,
 SD_{Final} = Standard deviation of post-treatment score,
Corr = Correlation between pre-treatment and post-treatment scores.

Based on evidence from existing literature, a correlation of 0.69 between pre-treatment scores (baseline) and post-treatment scores (final/endpoint) was used to calculate effect sizes.^{55,75} When sensitivity of potential correlation factors (0.0, 0.3, 0.5) was carried out, effect size estimates were found to be essentially unchanged. The Cochran's Q ($\alpha=0.10$) and I^2 statistics were employed to quantify the statistical heterogeneity between studies, where $p<0.10$ indicates a high level of statistical heterogeneity between studies. Sensitivity analyses were also performed on the type of intervention and study risk of bias, and by removing the studies with obvious between-group baseline imbalance to evaluate statistical stability and effect on statistical heterogeneity.

Although summary estimates for groupings of interventions were computed, we did not present the summary estimates because of the presence of high statistical heterogeneity or because of clinical heterogeneity (predominately related to differing dosage parameters, types of interventions, and study populations).

Rating the Body of Evidence

The strength of evidence (SOE) was assessed for each KQ using the EPC method for intervention studies, which is based on methods developed by the GRADE Working Group.⁷⁶ 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. Several domains of quality across studies may influence the overall SOE for these KQs, including:

1. Risk of bias (how the study design and conduct may have contributed to systematic error). This is judged as high, moderate, or low risk of bias.
2. Consistency of results (concerns homogeneity in direction and magnitude of results across different studies). In the context of intervention studies, this is the degree of heterogeneity of the summary effect size and can be evaluated with statistical tests of heterogeneity; these tests evaluate the null hypothesis that all studies in the meta-analysis have the same underlying magnitude of effect. When no summary effect size estimate is possible, then how widely the point estimate varies across studies and the degree of overlap between confidence intervals across studies was considered.⁷⁵ The importance of the direction relative to the magnitude of the effect will be judged for each group of interventions and outcomes.⁷⁷
3. Directness of the evidence (concerns whether the evidence being assessed reflects a single, direct link between the interventions of interest (tinnitus treatment) and the ultimate health outcome under consideration). Directness also applies to comparisons between interventions. For intervention studies, consideration should be given to how similar the test or the treatment is being used in practice reflecting the external validity or generalizability of the intervention.
4. Precision refers to the degree of certainty surrounding an effect estimate for each outcome (i.e., width of confidence intervals (CI)) for diagnostic accuracy outcomes, and treatment outcomes monitoring; this domain is related to study sample size and number of events).⁷⁷
5. Other key domains (publication bias, dose-response association, and strength of association [i.e., magnitude of effect]) were all considered when relevant). From these dose-response and strength of association were not considered with respect to downgrading the evidence.

We assessed the SOE for the six outcomes of benefit: TSQoL, perceived loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global quality of life, as well as outcomes of harm. The SOE was classified into four grades based on the AHRQ EPC Program approach: high, moderate, low, or insufficient^{76,78} as follows:

High quality SOE: Further research is very **unlikely** to change the confidence in the estimate of effect.

High SOE indicates that there are **consistent** findings (direction of effect and magnitude of effect) among 80% of the included comparative studies (RCT, CCT) with **low risk** of bias that are **generalizable** to the population in question. There are sufficient data (greater than 30 patients per intervention group for 80% of the included studies), with narrow confidence intervals. There are no known or suspected reporting or publication

biases. Criteria for determining that there are no serious threats to validity are met in all domains (studies are at low risk of bias, consistent, direct, precise, and free of reporting and publication bias).

Moderate quality SOE: Further research is **likely** to have an important impact on the confidence in the estimate of effect and may change the estimate.

The majority of studies (80 % of included studies for each outcome) are at high or medium risk of bias or criteria for **one** of the other domains (consistency, precision, directness, or publication bias) is not met.

Low quality SOE: Further research is **very likely** to have an important impact on the confidence in the estimate of effect and is likely to change the estimate.

Criteria for **two** of the domains are not met **or** there are serious concerns in a single domain that affect the validity of the results.

Insufficient quality evidence: An estimate of effect is very uncertain. Criteria for at least **three** domains are not met.

No evidence: No comparative studies were identified that evaluated any the outcome of interest (since the quality is evaluated for each outcome).

Judgment of study limitations was anchored by the presence of a minimum of one RCT with a rating of ‘good’, or a rating of greater than 7 points from 12, indicating low risk of bias. For a number of interventions, there is only a single study result to be reported. For those, the consistency is unknown; similarly, for single studies the precision was rated as unknown.

Consistency for the remaining groupings was judged within the SOE tables, on the stability of the direction of the effect (favoring treatment or favoring control) based on the point estimate and the degree of overlap between confidence intervals.

For small sample sizes (30 or less per treatment group) and wide confidence intervals, all the intervention groupings were ranked as being imprecise.

For most interventions, fewer than 10 studies were eligible and as such publication bias could not be formally assessed using statistical approaches. The risk of publication bias is greater for reviews that are based on small randomized trials.⁷⁹ Based on this potential risk, it was assumed that all intervention groupings were at risk in this systematic review and rated all groupings as “suspected” for publication bias.

Peer Review and Public Comment

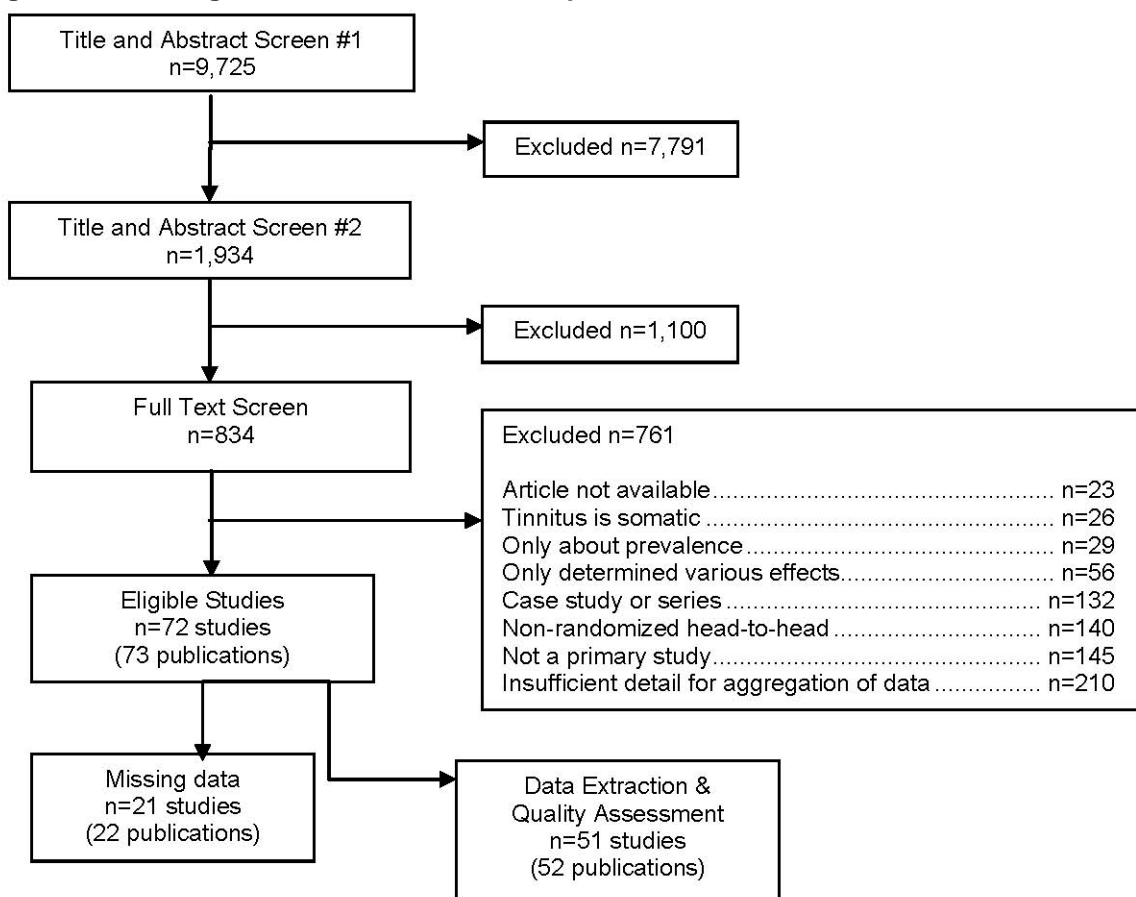
Experts in audiology, epidemiology, medical specialties, researchers and individuals representing stakeholder and user communities were invited to provide external peer review of this CER. The AHRQ TOO and an associate editor also provided comments on the report. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. All reviewer comments have been considered and the text revised. A disposition of comments report will be made available on the AHRQ website 3 months after the posting of the final report.

Results

Figure 2 provides details of the flow of studies and the final papers for review for the Key Questions (KQ).⁸⁰ The search yielded 9,725 unique citations. This includes five citations added as a result of the grey literature search (one from the Scientific Information Packages (SIPs) that were received, (two from clinical trial registries and two from conference abstracts). During two levels of title and abstract screening, 8,891 articles were excluded. A total of 834 citations proceeded to full text screening. After the final eligibility screening, 73 publications passed through full text screening. From these, 52 publications (51 studies) were eligible for data extraction for KQ2. Appendix C contains the list of studies excluded at full text screening.

Not included in the results, 22 reports (21 studies) did not present measures of variance¹²³⁻¹³⁹ or they presented results as proportions.¹⁴⁰⁻¹⁴⁴ Details of these studies may be found in Appendix D.

Figure 2. Flow diagram of citations in the Comparative Effectiveness Review of tinnitus



KQ1. In patients with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds, etc.) what is the comparative effectiveness of methods used to identify patients for further evaluation or treatment?

No studies addressing this question were identified in the literature search.

KQ2. In adults with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral interventions, including combinations of interventions?

A total of 51 studies (52 included publications)^{10,17,18,28,35,53,57,61,62,64,81-122} address KQ2. We organized the eligible studies based on intervention groupings suggested by the Technical Expert Panel. Results for this comparative effectiveness review (CER) are organized by type of intervention (i.e., pharmacological/food supplement; medical; sound technologies; and, psychological/behavioral). Within each intervention section, the discussion of the data is then organized by the primary outcomes: tinnitus-specific quality of life (TSQoL), perceived loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global quality of life.

From the 51 eligible studies (52 publications), 21 studies (and one companion publication¹²³) were not included in the results because they did not present measures of variance¹²³⁻¹³⁹ or they presented results as proportions.¹⁴⁰⁻¹⁴⁴ Where possible, forest plots were created for each outcome within the four groups of interventions showing the different treatments relative to inactive control. Forest plots for head-to-head trials were not generated as none of the active comparators were similar.

Pharmacological or Food Supplement Interventions

Key Messages

Thirteen of 16^{28,82,85,86,90,93,106,107,109,111,113-115,117,119,122} studies had sample sizes less than 100 and most did not contain sample size calculations. Authors did not specify minimum clinically worthwhile differences on outcome measurement instruments. The ability of the instruments used to discriminate between treatment effects across study groups was questionable.

Tinnitus-Specific Quality of Life

- Nortriptyline, sertraline, acamprosate, and Deanxit were shown to produce some improvement in TSQoL. All comparisons were against placebo (participants in the Deanxit study received 1 mg clonazepam in addition to Deanxit or placebo).
- However, strength of evidence (SOE) was insufficient for all comparisons because of medium risk of bias and inconsistent and imprecise effect estimates.

Subjective Loudness

- Neurotransmitter drugs showed improvement in subjective loudness versus placebo; however SOE was low because risk of bias was medium and effect estimates were imprecise.
- SOE was insufficient for the anti-depressant, other drug, and food supplement groups (single studies in each of these groups evaluated the outcome).

Sleep Disturbance

- Paroxetine and vardenafil showed improvement in sleep disturbance versus placebo; no improvement was observed with Deanxit.
- However, SOE was insufficient because only one study for each intervention considered this outcome.

Depression Symptoms

- Sertraline, paroxetine, and nortriptyline showed improvements in depression symptoms versus placebo; however, SOE was insufficient because the risk of bias was moderate and effects were inconsistent and imprecise.
- Improvements were also seen in honeybee larvae versus hydrogenated dextrin; however, SOE was insufficient because only one honeybee larvae study evaluated this outcome.

Global Quality of Life

- Only sertraline showed improved global quality of life versus placebo; however, SOE was insufficient for all anti-depressants (sertraline, paroxetine, trazodone) versus placebo because the risk of bias was moderate and effects were inconsistent and imprecise.
- SOE was insufficient for acamprosate, vardenafil, and ginkgo biloba versus placebo because only one study for each intervention considered this outcome.

Characteristics of Included Studies

A total of 17 articles^{28,82,85,86,90,93,99,106,107,109,111,113-115,117,119,122} reported on 16 unique studies that evaluated interventions in the pharmacological or food supplement domain (Table 3; Appendix E, Table E1). Two articles^{99,122} pertained to the same study, with the followup publication⁹⁹ containing additional data on global quality-of-life (QoL) as an outcome.

Population Duration and Severity

In ten studies,^{82,93,106,107,111,113,115,117,119,122} the majority of participants were male. The percentages of male participants in these studies ranged from 52 percent¹¹⁵ to 89 percent.¹⁰⁷ Females formed the majority of participants in four studies,^{85,86,90,109} ranging from 59 percent⁸⁶ to 79 percent.⁸⁵ One article¹¹⁷ reported a male:female ratio of 2:1 in the active treatment group and 1.5:1 in the placebo group. Two publications^{28,114} did not report the percentages of males and females in the study populations.

All of the studies were conducted in primarily middle-age populations. Mean ages in 14 studies ranged from 42¹²² to 63.⁸⁵ One study⁹⁰ reported that 53 percent of participants were at least 60 years of age; another indicated that all participants fell within an age range of 18 to 65 years.²⁸

The largest study analyzed data for 708 participants at the end of followup.⁹³ The remaining 15 studies contained a mean of 62 participants, ranging in size from 28 persons¹⁰⁷ to 95 persons.¹⁰⁹

Intervention

Four studies (five publications)^{90,99,113,115,122} investigated anti-depressant drugs versus placebo. These drugs included sertraline,^{99,122} paroxetine,¹¹³ trazodone,⁹⁰ and nortriptyline.¹¹⁵ Dosage levels in the sertraline, paroxetine, and nortriptyline articles were at the recommended levels for treating depression. However, the dosage level in the trazodone study was below the recommended dose for depression; the dosage level was instead suitable for use as a sleep aid. Five publications^{28,82,109,114,119} involving placebo comparators examined neurotransmitter drugs that enhance or stimulate γ -aminobutyric acid (GABA). The neurotransmitter drugs were gabapentin,¹⁰⁹ baclofen,¹¹⁹ alprazolam,²⁸ and acamprosate.^{82,114} Three studies investigated other drugs, including methylprednisolone versus placebo,¹¹⁷ vardenafil versus placebo,¹⁰⁶ and Deanxit versus placebo (all participants received 1 mg clonazepam in addition to Deanxit or placebo).¹⁰⁷

Four papers evaluated food supplements, with two^{93,111} focused on ginkgo biloba, one⁸⁶ on zinc, and one⁸⁵ on honeybee larvae. All food supplements were compared to placebo (which was hydrogenated dextrin in the larvae study).

Mean length of followup was 11 weeks. The shortest followup period was 3 weeks¹¹⁹ and the longest was 16 weeks.¹²²

Comparators

Table 3 shows the interventions and comparators for studies in this grouping.

Table 3. Interventions and comparators used in studies that evaluate pharmacological and food supplement interventions and outcomes

Pharma/Food Intervention	#	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects
Anti-depressant drugs		INACTIVE COMPARATOR							
	1	Sertraline (SSRI antidepressant) vs. placebo Zoger, ¹²² 2006 and Holgers, ⁹⁹ 2011		HAS ⁻ , CPRS-S-A, PGWB-sub	HDS ⁻ , CPRS-S-A, PGWB-sub	VAS	PGWB	TSQ ⁺ VAS	Yes
	2	Paroxetine (SSRI antidepressant) vs. placebo Robinson, ¹¹³ 2005	PSQI	HADS-A, BAI ⁺	HADS-D, BDI ⁺		QWB	THQ ⁺ , Likert-scale	Yes
	3	Trazodone (SARI antidepressant) vs. placebo Dib, ⁹⁰ 2007					VAS	VAS-s ⁺ VAS-d	Yes
	4	Nortriptyline (2 nd gen tricyclic antidepressant) vs. placebo Sullivan, ¹¹⁵ 1993		Sheehan's Disability	HDS			IOWA ⁺ , Likert-scale	Yes
Neuro-transmitter drugs		INACTIVE COMPARATOR							
	1	Gabapentin (GABA analogue – GABAergic) vs. placebo Piccirillo, ¹⁰⁹ 2007						THI	Yes
	2	Baclofen (selective GABAB1 receptor agonist) vs. placebo Westerberg, ¹¹⁹ 1996				Subjective		THI	Yes
	3	Alprazolam (benzodiazepine – anxiolytic) vs. placebo Johnson, ²⁸ 1993				VAS			Yes
	4	Acamprosate (glutamate antagonist & GABA agonist) vs. placebo Sharma, ¹¹⁴ 2012				VAS	Subjective		None
	5	Acamprosate vs. placebo Azevedo 2005, ⁸² 2005						Subjective	Yes
Other drugs		INACTIVE COMPARATOR							
	1	Methylprednisolone (intratympanic injection) vs. placebo Topak, ¹¹⁷ 2009				Self-rated		TSI	Yes
	2	Vardenafil (PDE5 inhibitor) vs. placebo Mazurek, ¹⁰⁶ 2009	TQ-sub				SF-36	TQ	Yes
	3	Deanxit vs. placebo Meeus, ¹⁰⁷ 2011	TQ-sub		BDI	VAS		TQ VAS-Ann	None

Table 3. Interventions and comparators used in studies that evaluate pharmacological and food supplement interventions and outcomes (cont'd)

Pharma/Food Intervention	#	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects
<i>Food supplements</i>		INACTIVE COMPARATOR							
	1	Gingko Biloba vs. placebo Rejali, ¹¹¹ 2004					GHSI	THI	Yes
	2	Gingko vs. Placebo: only effect size reported Drew, ⁹³ 2001				VAS		TSQ (21-item)	Yes
	3	Enzymolyzed honey bee larvae vs. placebo, Aoiki, ⁸⁵ 2012			THI-subscale			THI, VAS	Yes
4	Zinc vs. placebo Arda, ⁸⁶ 2003				Subjective			Yes	

Abbreviations: Ann = annoyance; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CPRS-S-A = Comprehensive Psychopathological Rating Scale – Anxiety subscale; GABAB1 = gamma-aminobutyric acid B1; gen = generation; GHSI = Glasgow Health Status Inventory; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale – Depression subscale; HAS = Hamilton Anxiety Rating Scale; HDS = Hamilton Depression Rating Scale; IOWA = IOWA disability scale for Tinnitus; HDS = Hospital Depression Scale; PDE5 = phosphodiesterase type 5; Pharma = Pharmacological; PGWB = Psychological General Well-Being index; PSQI = Pittsburg Sleep Quality Index; QoL = Quality of Life; QWB = Quality of Well-being Scale; SARI = serotonin antagonist reuptake inhibitor; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; SSRI = selective serotonin reuptake inhibitor; THI = Tinnitus Handicap Inventory; THQ = Tinnitus Handicapped Questionnaire; TQ = Tinnitus Questionnaire; TSI = Tinnitus Severity Index; TSQ = Tinnitus Severity Questionnaire; VAS = visual analogue scale; vs. = versus

*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Outcomes

Of the six outcomes of interest, tinnitus-specific QoL was evaluated in 13 studies,^{82,85,90,93,106,107,109,111,113,115,117,119,122} subjective loudness in eight studies,^{28,86,93,107,114,117,119,122} sleep disturbance in three studies,^{106,107,113} anxiety symptoms in three studies,^{113,115,122} depression symptoms in five studies,^{85,107,113,115,122} and global QoL in six studies (Table 4).^{90,106,111,113,114,122} Adverse effects were reported in all except two studies.^{107,114} See Table 3 and Appendix E, Table E1.

Table 4. Outcome measurements used in pharmacological and food supplement intervention studies

Outcome	Outcome Measurement Used
Sleep disturbance	PSQI (Pittsburg Sleep Quality Index) ¹¹³ TQ-subscale (Tinnitus Questionnaire subscale – sleep disturbance) ^{106,107}
Anxiety symptoms	HADS-A (Hospital Anxiety and Depression Scale – Anxiety subscale) ^{99,113} CPRS-S-A (Comprehensive Psychopathological Rating Scale – Anxiety subscale) ⁹⁹ PGWB-subscale (Psychological General Well-being Index) ⁹⁹ BAI (Beck Anxiety Inventory) ¹¹³ Sheehan's Disability Scale ¹¹⁵
Depression symptoms	HADS-D (Hospital Anxiety and Depression Scale – Depression subscale) ^{99,113} HDS (Hospital Depression Scale) ¹¹⁵ CPRS-S-A (Comprehensive Psychopathological Rating Scale – Anxiety subscale) ⁹⁹ PGWB-subscale (Psychological General Well-being Index) ⁹⁹ BDI (Beck Depression Inventory) ^{107,113} THI-subscale (Tinnitus Handicap Inventory subscale) ⁸⁵
Subjective loudness	VAS (Visual Analogue Scale) ^{28,93,99,107,114} Self-rated/subjective ^{86,117,119}
Global quality of life	PGWB (Psychological General Well-being Index) ^{99,122} QWB (Quality of Well-being Scale) ¹¹³ VAS (Visual Analogue Scale) ⁹⁰ SF-36 ¹⁰⁶ GHSI (Glasgow Health Status Inventory) ¹¹¹ Subjective/self-rated ¹¹⁴
Tinnitus-specific quality of life	TSQ (Tinnitus Severity Questionnaire) ^{93,99} THQ (Tinnitus Handicapped Questionnaire) ¹¹³ TQ (Tinnitus Questionnaire) ^{106,107} VAS (Visual Analogue Scale) ^{85,90,99,107} IOWA (IOWA disability scale) ¹¹⁵ THI (Tinnitus Handicap Inventory) ^{85,109,111,119} TSI (Tinnitus Severity Index) ¹¹⁷ Likert-scale ^{113,115} Subjective/self-rated ⁸²

Setting

Twelve studies^{28,86,106,107,109,111,113-115,117,119,122} were set in specialty clinics (i.e., ear-nose-throat). Three studies^{82,85,109} recruited participants through a university hospital, and another⁹³ through advertisements in the national press or a tinnitus publication. One study⁹⁰ did not report its setting.

Country

The studies were carried out in several different countries: Sweden;¹²² the United States;^{28,109,113,115,119} Brazil;^{82,90} India;¹¹⁴ Germany;¹⁰⁶ Belgium;¹⁰⁷ United Kingdom;^{93,111} Japan;⁸⁵ and Turkey.^{86,117}

Sources of Funding

Sources of funding were not reported in seven publications.^{28,82,86,90,111,114,117} In one of these studies, the author holds a patent for the use of the drug in Tinnitus.⁸² Ten publications received funding from research councils, foundations, and government departments and non-profit associations.^{85,93,106,107,109,113,115,119,122}

Risk of Bias for Pharmacological and Food Supplement Interventions

The risk of bias, taken across all of the studies, was low to medium (Figure 3). Most of the major issues related to bias, assessed via the Jadad scale and supplemental questions on allocation concealment, intention-to-treat analysis, and justification of sample size, were related to reporting. All of the studies were RCTs, yet the authors of 9 publications did not describe the randomization procedure. In only one instance⁸⁵ could we ascertain that the randomization method was inappropriate, i.e., the authors described it as an ‘alternating sequence’ based on 1:1 assignment into groups. Randomization procedures were appropriate in 6 studies.^{93,106,109,111,113,122}

Related to randomization is the issue of allocation concealment, i.e., the method(s) used to ensure that the randomization sequence remains hidden from the person(s) responsible for recruiting participants into studies. Nine studies^{85,86,90,93,106,109,113,117,122} reported, and seven^{28,82,107,111,114,115,119} did not report, the methods of allocation concealment. The methods in two studies were judged to be inappropriate.^{86,117}

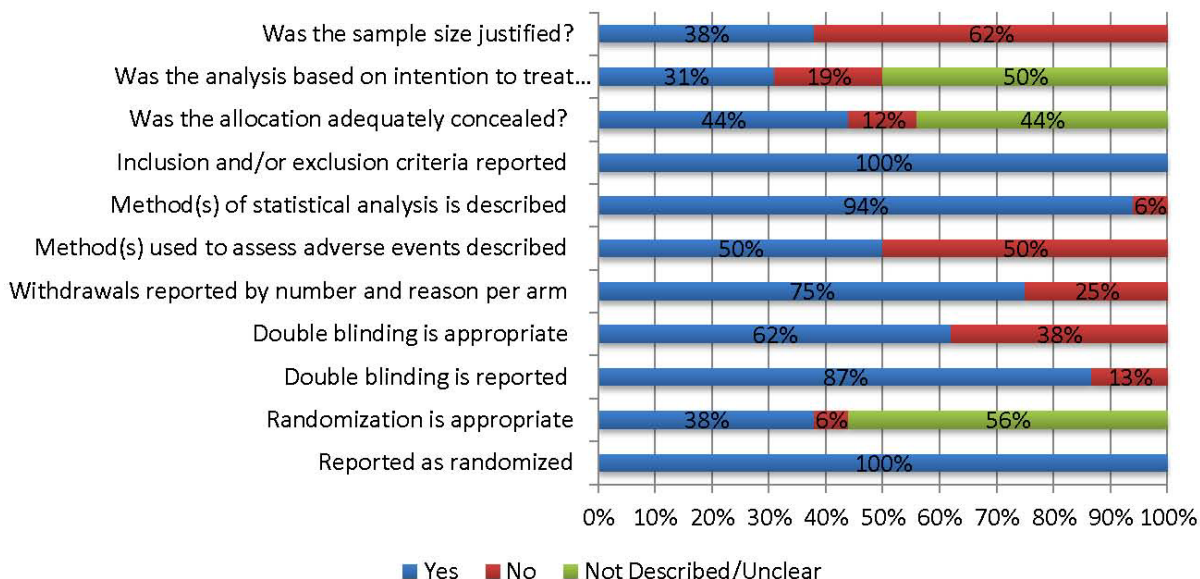
Fourteen studies contained specific mention of double-blinding. In four of these studies,^{82,107,111,114} the authors did not provide sufficient detail for us to assess whether the methods of double-blinding were appropriate. The two studies without double-blinding included the methylprednisolone trial¹¹⁷ (single-blinded) and one of the zinc studies⁸⁶ (no blinding reported whatsoever).

Only half the studies^{28,93,106,109,113,117,119,122} reported the methods used to assess adverse effects. Since knowledge of adverse effects is necessary to support clinical decision making, which requires the consideration of benefits and harms,¹⁴⁵ researchers must pay careful attention to how they ascertain these effects. Failure to report the methods in this regard raises the possibility that adverse effects were assessed in an ad hoc or unsystematic fashion, or not at all. Six studies^{82,85,86,90,107,111,115} that did not delineate methods for assessing adverse effects did actually report such effects. Two studies stated that there were no adverse effects reported.^{107,114}

Five studies^{106,109,113,119,122} reported that participants were analyzed according to an intention-to-treat principle. Many of the other studies appeared to follow an intention-to-treat principle as well. RCTs should be analyzed using this principle to promote the unbiased assessment of efficacy in light of the extent to which study participants adhere to treatment.¹⁴⁶ Given the added potential for bias when RCTs are not analyzed according to the intention-to-treat principle, authors should be clear about the methods they have used to analyze trial data.

Ten trials^{28,82,86,90,106,107,114,115,117,119} did not contain a justification for sample size. Since all except three studies contained samples of less than 100 persons, readers could legitimately raise the question of whether the studies had sufficient power to detect clinically important effects.

Figure 3. Distribution of methodological risk of bias criteria of randomized controlled trials for the pharmacological and food supplement interventions



Results for Pharmacological or Food Supplement Interventions by Outcome

Tinnitus-Specific Quality of Life

Four studies^{82,107,115,122} assessed tinnitus-specific QoL by measuring discomfort, disturbance, or annoyance. Eleven studies^{85,93,106,107,109,111,113,115,117,119,122} examined tinnitus-specific QoL by measuring severity. One study used both.⁹⁰ See Table 3 and Appendix E, Table E1.

All five studies^{82,90,107,115,122} examining discomfort, disturbance, or annoyance used some form of visual analogue or Likert-type scale to measure the outcome. The sertraline study¹²² used a 100 mm visual analogue scale (VAS) and found no statistically significant difference between groups. The trazodone study⁹⁰ employed a 0- to 10-point scale and also found no difference between groups. Conversely, a paper⁸² describing results in 41 persons given acamprosate (333 mg taken 3 times daily) or placebo reported that 86.9 percent of participants receiving the active medication showed improvement (any reduction in score) on a 1- to 10-point ‘disturbance’ scale, which compared favorably to the 44.4 percent of participants in the placebo group who showed improvement (p=0.004). If improvement was defined as a 50 percent or greater reduction in score, then 47.8 percent in the acamprosate group and 11.1 percent in the placebo group were improved over followup (p=0.012). Note that two of the study authors hold the patent on use of acamprosate for tinnitus.

In the Deanxit crossover trial,¹⁰⁷ discomfort was measured on a 0 to 100 VAS scale. Persons who received Deanxit after placebo (instead of placebo after Deanxit) showed improvement on the VAS at the end of followup (mean difference in score from baseline=9.5; p=0.024) (Figure 4). This study¹⁰⁷ also used a Hyperacusis Questionnaire to assess annoyance and the authors reported that they did not find any significant between-group differences on this scale (no statistics presented in the publication).

The nortriptyline study¹¹⁵ used a battery of instruments to measure discomfort. These instruments included the Multidimensional Pain Inventory (MPI) self and spouse evaluations, two VAS which measure life disruptions due to tinnitus (one examining ‘internally referred’ disruptions, another ‘externally referred’ disruptions), and a 5-point overall tinnitus disruption scale. The active treatment group had lower (better) mean scores on all instruments except the MPI spouse evaluation, with mean differences in score being significant on the MPI self-evaluation (mean difference=0.6; $p<0.01$) and VAS internal disruption (mean difference=0.9; $p<0.05$) (Figure 4).

Turning to the 12 studies^{85,90,93,106,107,109,111,113,115,117,119,122} that measured tinnitus-specific QoL as severity, a multitude of different instruments were used to assess the outcome. In 10 studies, between group differences were not statistically significant at the 5 percent level on the following instruments: Tinnitus Handicap Questionnaire (and a supplemental 8-point Likert scale, as well as the Disability Inventory),¹¹³ 10-point VAS,^{85,90} Iowa Disability Scale,¹¹⁵ Tinnitus Handicap Inventory,^{109,111,119} Tinnitus Severity Index,¹¹⁷ Tinnitus Questionnaire,¹⁰⁶ and a 21-item severity questionnaire based on existing instruments.⁹³

In the sertraline study,¹²² the treated group experienced greater reductions in severity over 16 weeks of followup relative to the placebo group, as evidenced by larger mean changes in score on the Tinnitus Severity Questionnaire (i.e., 4.69 vs. 2.12; $p=0.024$).

In the Deanxit crossover trial,¹⁰⁷ the authors subtracted mean scores on the Tinnitus Questionnaire after 7 weeks of followup from baseline scores. They reported that mean changes in score were higher in the group that received placebo followed by Deanxit (mean score change=11.0; $p<0.001$), compared to the group that received Deanxit followed by placebo (mean score change=7.9; $p=0.001$). However, conclusions about efficacy from this study are limited because the authors were investigating the sequence of treatment rather than a direct comparison of the effects of Deanxit versus placebo.

Strength of Evidence—Tinnitus-Specific Quality of Life

Strength of evidence was insufficient for tinnitus-specific QoL in the case of each intervention group (antidepressants, neurotransmitter drugs acting on GABA, other drugs and food supplements) relative to placebo comparators. Only honeybee larvae (versus hydrogenated dextrin) had other than a placebo comparator and SOE was also insufficient (Table 5). Effect sizes were inconsistent regarding direction of effect; included studies, when taken together, had medium risk of bias. Each intervention group was rated ‘imprecise’ under the precision domain because of small sample sizes and a lack of power calculations in the majority of included studies, as well as the heterogeneity of the interventions. Additionally, the published reports presented no evidence for dose response and the risk of publication bias was high given the small sample sizes.

Table 5. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report tinnitus-specific quality of life outcomes

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Anti-depressants	Nortriptyline Paroxetine Sertraline Trazodone	4 ^{*90,99,113,115,122}	Medium	Inconsistent	Direct	Imprecise	-0.61 (-1.03 to -0.19) to 0.12 (-0.31 to 0.54)	Insufficient
Neuro-transmitter drugs	Acamprosate Baclofen Gabapentin	3 ^{82,109,119}	Medium	Inconsistent	Direct	Imprecise	-1.57 (-2.28 to -0.86) to -0.01 (-0.38 to 0.35)	Insufficient
Other drugs	Deanxit, MEP, varденаfil	3 ^{106,107,117}	Medium	Inconsistent	Direct	Imprecise	-0.68 (-1.21 to -0.16) to 0.35 (-0.26 to 0.86)	Insufficient
Food supplement	Gingko biloba Honeybee larvae	3 ^{85,93,111}	Medium	Inconsistent	Direct	Imprecise	-0.21 (-0.72 to 0.30) to -0.21 (-0.72 to 0.30)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference

Note: all drugs were compared to placebo except honeybee larvae (versus hydrogenated dextrin); Deanxit comparison was a crossover trial of Deanxit versus placebo, with each participant given 1 mg clonazepam in addition to Deanxit or placebo.

*four studies, five publications

Subjective Loudness

Eight publications^{28,86,93,107,114,117,119,122} examined loudness, primarily using subjective VAS-type scales (Tables 3 and 4). In two studies,^{86,122} active treatments had more impact on loudness than comparators. A group receiving sertraline had a greater mean reduction in score over the course of followup, measured on a 100 mm VAS, than placebo (15.21 vs. 5.15; p=0.014).¹²² A study comparing zinc (50 mg/day for 8 weeks) to placebo in 41 persons seen at ear-nose-throat clinics found the mean score to be 1.41 points lower in the zinc group (p<0.05) after 8 weeks of followup, as measured using a 7-item subjective loudness questionnaire (higher scores indicated more loudness).⁸⁶

Four studies failed to find any differences (p>0.05) in loudness between treatment arms. These studies included baclofen (10 to 30 mg/day twice daily for 3 weeks) vs. placebo in 58 persons recruited from a tinnitus referral center (subjective 10-point scale),¹¹⁹ methylprednisolone solution (0.3 to 0.4 ml intratympanic injection of 62.5 mg/ml methylprednisolone) vs. saline in 59 persons recruited from an unreported setting (subjective 10-point scale),¹¹⁷ Deanxit vs. placebo (0 to 100 VAS),¹⁰⁷ and ginkgo biloba (50 mg given 3 times daily) vs. placebo in persons who were recruited through advertisements placed in the national press and a tinnitus publication (6-point loudness scale) (Figure 5).⁹³

In a study²⁸ of alprazolam (25 to 50 mg/day) versus placebo in 36 persons recruited from a tinnitus registry and followed for 12 weeks, loudness was measured using a 10-point VAS and Norwest SG-1 tinnitus synthesizer. The authors did not provide between-group comparisons on

each outcome; however, they stated that four of 17 persons in the alprazolam group, and 18 of 19 persons in the placebo group, experienced stable or increased loudness on either the VAS or synthesizer. Using these data, one may compute a relative risk of 0.25 (95% CI, 0.10 to 0.59), which means that the risk of stable or increased loudness was 75 percent less in the alprazolam group compared to the placebo group.

A crossover trial¹¹⁴ of acamprosate (333 mg twice daily for 45 days) versus placebo in 40 persons who were outpatients at an ear-nose-throat hospital measured loudness on a 10 cm VAS. The authors only present within-group comparisons in the text, but do mention that 92.5 percent of the treated group, and 12.5 percent of the placebo group, displayed improvement over the course of followup. However, the authors do not define improvement, which appears to be an amalgam of the loudness and global QoL outcomes. Nor do the authors conduct a statistical test to compare improvement between the two groups.

Strength of Evidence—Subjective Loudness

The SOE is insufficient for the anti-depressant, other drug, and food supplement groups because only use one study in each group could be used to make judgments about SOE. In the neurotransmitter drugs group, SOE is low, despite the fact that consistency across the results in three studies suggests benefits for these drugs. Risk of bias for the neurotransmitter drugs is medium and effect estimates are imprecise due to small sample sizes, a lack of power calculations, and the heterogeneity of the interventions. Additionally, all eight published reports presented no evidence for dose response and the risk of publication bias was high given the small sample sizes (Table 6).

Table 6. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report subjective loudness outcomes

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Anti-depressants	Sertraline	1 ^{99,122}	Low	Unknown (single study)	Direct	Imprecise	-0.45 (-0.95 to 0.05)	Insufficient
Neurotransmitter drugs	Baclofen, alprazolam acamprosate	3 ^{28,114,119}	Medium	Consistent	Direct	Imprecise	-2.08 (-2.87 to -1.30) to -0.29 (-0.79 to 0.22)	Low
Other drugs	MEP, Deanxit	2 ^{107,117}	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study ¹⁰⁷)	Direct	Imprecise	-0.07 (-0.58 to 0.44)	Insufficient
Food supplement	Gingko biloba Zinc	2 ^{86,93}	Medium	Unknown (single study) (Cannot calculate SMD in zinc study ⁸⁶)	Direct	Imprecise	-0.91 (-1.60 to -0.22)	Insufficient

Abbreviations: CI = confidence interval; MEP = methylprednisolone injections; n = number; SOE = strength of evidence; SMD = standard mean difference

Note: all drugs were compared to placebo; Deanxit comparison was a crossover trial of Deanxit versus placebo, with each participant given 1 mg clonazepam in addition to Deanxit or placebo.

^{*} one study, two publications

Sleep Disturbance

Three studies looked at the outcome of sleep disturbance (Tables 3 and 4). One study¹¹³ investigating sleep compared paroxetine (50 mg/day) and placebo in 115 persons over 14 weeks of followup. Between-group differences in sleep quality, measured using the Pittsburg Sleep Quality Index (PSQI), were not statistically significantly different at the end of followup. Two studies^{106,107} examined sleep using the sleep disturbance subscale of the Tinnitus Questionnaire (TQ). The first¹⁰⁶ of these two studies compared vardenafil (10 mg taken twice daily) against placebo and found no between-group differences ($p=0.88$) on the sleep disturbance subscale. The second of these two studies, a crossover trial¹⁰⁷ of Deanxit (flupentixol 0.5 mg and melitracen 10 mg) and clonazepam (1 mg), compared to placebo and clonazepam, reported decreases in score following the first treatment phase, and increases in score following the second treatment phase, regardless of whether Deanxit or placebo was received first. However, the authors do not report a statistical comparison of these subscale results (Figure 6).

Strength of Evidence—Sleep Disturbance

The SOE is insufficient for sleep disturbance because we could only use one study in each of the two relevant intervention groups to make judgments about SOE (Table 7). In the other drug intervention group, studies of vardenafil¹⁰⁶ and Deanxit¹⁰⁷ were included in the review. However, the Deanxit study could not be used to assess SOE because the authors compared baseline scores to treatment order, i.e., whether participants received Deanxit before or after placebo. Thus, the comparison did not evaluate the efficacy of Deanxit versus placebo.

Table 7. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report sleep disturbance outcomes

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Anti-depressant	Paroxetine	1 ¹¹³	Low	Unknown (single study)	Direct	Imprecise	0.31 (-0.06 to 0.67)	Insufficient
Other drugs	Vardenafil, Deanxit	2 ^{106,107}	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study ¹⁰⁷)	Direct	Imprecise	-0.09 (-0.69 to 0.52)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference

Note: all drugs were compared to placebo; Deanxit comparison was a crossover trial of Deanxit versus placebo, with each participant given 1 mg clonazepam in addition to Deanxit or placebo.

Anxiety Symptoms

Three placebo-controlled studies^{113,115,122} included anxiety as an outcome (Tables 3 and 4). Two studies (sertraline,¹²² paroxetine¹¹³) measured anxiety with the Hamilton Anxiety Rating Scale (HAS); one study¹¹³ also utilized the Beck Anxiety Inventory (BAI). The third study,¹¹⁵ of nortriptyline (50 to 150 mg/mL for 6 weeks) versus placebo, used Sheehan's Disability Scales (SDS). The paroxetine study¹¹³ found greater improvements in score for the placebo group on the HAS and BAI, although the differences were not statistically significant. Conversely, a study¹²² of sertraline (50 mg/day) versus placebo in 63 persons found the mean score change over followup on the HADS to be larger in the treated group compared to the placebo group (8.51 vs.

4.09; p=0.04). On the SDS,¹¹⁵ the nortriptyline group showed slight improvement relative to the placebo group, but the difference was not statistically significant.

The sertraline study¹²² also measured anxiety using the Comprehensive Psychopathological Rating Scale (CPRS) anxiety subscale and in a companion paper,⁹⁹ the Psychological General Well-being Index (PGWB), which contains an anxiety subindex. Over the course of followup, the sertraline group displayed a larger mean score change on the CPRS relative to the placebo group (4.38 vs. 0.73; p=0.013), which indicates a greater reduction in anxiety for persons receiving the active treatment. Likewise, the sertraline group also showed a larger mean score change versus the placebo group on the PGWB (4.59 vs. 0.61; p=0.002) (Figure 7).

Strength of Evidence—Anxiety Symptoms

The SOE is insufficient with regard to suggesting whether anti-depressants are more efficacious than placebo in reducing anxiety in persons with tinnitus. Risk of bias is medium, direction of effect estimates is inconsistent, and the certainty around effect estimates is imprecise due to small sample sizes and the heterogeneity of the interventions. Additionally, all three published reports presented no evidence for dose response and the risk of publication bias was high given the small sample sizes (Table 8).

Table 8. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report anxiety symptoms outcomes

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Anti-depressants	Sertraline Paroxetine Nortriptyline	3 ^{113,115,122}	Medium	Inconsistent	Direct	Imprecise	-1.13 (-1.57 to -0.69) to 0.28 (-0.09 to 0.64)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference; SSRI = serotonin reuptake inhibitors

Note: all drugs were compared to placebo

Depression Symptoms

Five studies considered depression, with two^{113,122} utilizing more than one outcome measure (Tables 3 and 4). Three^{113,115,122} of the five trials measured depression with the Hamilton Depression Rating Scale (HAM-D), two^{107,113} with the Beck Depression Inventory (BDI), one with the CPRS depression subscale and PGWB depression subindex,^{99,122} and one⁸⁵ with the depression question on the Tinnitus Handicap Inventory (THI). On the HAM-D, treated groups showed greater improvement than placebo when treated with sertraline (difference not significant)¹²² and nortriptyline (difference in mean score change over followup=3.7; p<0.05).¹¹⁵ In the sertraline study,^{99,122} the mean changes in score over followup on the CPRS depression subscale and PGWB depression subindex favored the treated group (CPRS: difference in mean change score=5.88, p=0.002; PGWB: difference in mean change score=2.22, p=0.002). For the paroxetine-placebo comparison,¹¹³ changes in score on the HAM-D and BDI were greater in the placebo group over the course of followup, although the differences were not statistically significant relative to the treated group. The authors of the Deanxit crossover¹⁰⁷ wrote that they did not find between-group differences on the BDI; however, they did not report any numerical results or statistical calculations.

The final study in this outcome domain⁸⁵ compared lyophilized powder of enzymolyzed honeybee larvae (720 mg given 4 times daily) to hydrogenated dextrin over 12 weeks of

followup. The authors administered the THI to the 58 study participants and found only one between-group difference after conducting subgroup analyses for each of the THI's 25 questions. On the depression question, the mean score difference at week 12 favored the honeybee larvae group (MSD=0.08; p<0.05) (Figure 8).

Strength of Evidence—Depression Symptoms

The SOE is insufficient that anti-depressants^{99,113,115,122} (Table 9) improve depression symptoms relative to placebo because the risk of bias was moderate, effects were inconsistent and imprecise, no evidence was reported about dose response relations, and the small sample sizes could have led to publication bias. SOE is insufficient for Deanxit¹⁰⁷ and honeybee larvae⁸⁵ because only one study evaluated each of these interventions.

Table 9. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report depression symptoms outcomes

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Anti-depressants	Sertraline Paroxetine Nortriptyline	3 ^{113,115,122}	Medium	Inconsistent	Direct	Imprecise	-1.13 (-1.57 to -0.69) to 0.21 (-0.16 to 0.57)	Insufficient
Other drugs	Deanxit	1 ¹⁰⁷	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study ¹⁰⁷)	Direct	Imprecise		Insufficient
Food supplement	Honeybee larvae	1 ⁸⁵	Medium	Unknown (single study)	Direct	Imprecise	-0.49 (-1.01 to 0.04)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference; SSRI = serotonin reuptake inhibitors

Note: all drugs were compared to placebo except honeybee larvae (versus hydrogenated dextrin); Deanxit comparison was a crossover trial of Deanxit versus placebo, with each participant given 1 mg clonazepam in addition to Deanxit or placebo

Global Quality-of-Life

Six studies examined global QoL (Tables 3 and 4)^{90,106,111,113,114,122} and only one study (sertraline¹²²) showed improvement versus placebo. The sertraline trial¹²² reported QoL results, measured using the PGWB, in a companion paper:⁹⁹ after 16 weeks of followup, the improvement in mean score compared to baseline was greater in the treated group relative to the placebo group (20.83 vs. 2.79; p=0.001). In four other studies, global QoL was assessed using the Quality of Well-being Scale,¹¹³ a 10-point VAS,⁹⁰ Short Form 36,¹⁰⁶ or Glasgow Health Status Inventory.¹¹¹ In these four studies, between-group differences in mean score changes over followup were extremely minimal and not suggestive of any particular direction of effect (Figure 9).

The acamprosate study¹¹⁴ utilized an unspecified QoL instrument that was linked to an incorrect citation. The authors combined outcomes and reported 92.5 percent improvement in the treated group and 12.5 percent improvement in the placebo group, although the paper does not indicate the portion of this improvement attributable to QoL.

Strength of Evidence—Global Quality-of-Life

The SOE is insufficient for anti-depressants versus placebo in global QoL, for the same reasons as outlined in the depression symptoms section above (Table 10). SOE is insufficient for acamprosate,¹¹⁴ vardenafil,¹⁰⁶ and ginkgo biloba¹¹¹ because only one study evaluated each of these interventions.

Table 10. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report global quality of life outcomes

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Anti-depressants	Sertraline Paroxetine Trazodone	3 ^{90,113,122}	Medium	Inconsistent	Direct	Imprecise	-0.24 (-0.60 to 0.13) to 1.06 (0.53 to 1.59)	Insufficient
Neuro-transmitter drugs	Acamprosate	1 ¹¹⁴	Medium	Unknown (single study)	Direct	Imprecise	1.53 (0.82 to 2.25)	Insufficient
Other drugs	Vardenafil	1 ¹⁰⁶	Low	Unknown (single study)	Direct	Imprecise	-0.22 (-0.83 to 0.38)	Insufficient
Food supplement	Ginkgo biloba	1 ¹¹¹	Medium	Unknown (single study)	Direct	Imprecise	-0.07 (-0.58 to 0.44)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference; SSRI = serotonin reuptake inhibitors

Note: all drugs were compared to placebo

Adverse Effects

Adverse effects spanned a range of clinical severity, from dry or sour mouth^{90,113} to confusion,¹¹⁹ but generally subsided after discontinuation of treatment (Table 11). Incidence of adverse effects varied from 3 percent¹²² to 67 percent.¹¹⁷ One study¹¹⁴ did not report adverse effects and one trial⁸⁵ only reported that 2 persons withdrew due to ‘discomfort’.

Among the anti-depressant trials, adverse effects were minimal in one trial,¹²² with one sertraline participant reporting sexual dysfunction and one placebo participant reporting an unspecified problem. Eighty-eight percent of participants in the trazodone study⁹⁰ were free of adverse effects with seven reported effects in the treated group, the most serious being hypertensive crisis, and three in the placebo group: sour mouth, insomnia, sleepiness. For paroxetine,¹¹³ eight different effects occurred during followup: sexual dysfunction, drowsiness, dry mouth, sweating, insomnia, gastrointestinal distress, tremor, and headache. The incidence of sexual dysfunction, drowsiness, and dry mouth were statistically significantly greater in the paroxetine group relative to the placebo group. One study¹¹⁵ reported anticholinergic effects and sedation.

Turning to neurotransmitter drugs, nine persons withdrew from the gabapentin study¹⁰⁹ due to nausea (n=3), weight gain (n=2), sleep disturbance (n=2), or dizziness (n=1). These persons were assigned to the active treatment group. The baclofen trial¹¹⁹ saw higher incidences (p<0.05) of confusion, dizziness, and drowsiness in the treated group, with no differences (p>0.05) between treatment and placebo groups in terms of gastrointestinal problems, weakness, or worsening tinnitus. Twelve of 17 persons who received alprazolam²⁸ reported side effects, including drowsiness (n=7), insomnia (n=1), difficulty functioning at work (n=1), or more dreams during sleep (n=4). The authors of the acamprosate trial⁸² indicated that 12 percent of the

acamprosate group and 20 percent of the placebo group reported adverse effects (p=0.35), which included epigastralgia and choking (no specific numbers reported).

In the methylprednisolone vs. saline study,¹¹⁷ the authors reported percentage incidences of four types of adverse effects, with higher percentages in the treated vs. placebo group: pain (67 vs. 52 percent; p>0.05); burning sensation (57 vs. 17 percent; p=0.002); vertigo (57 vs. 38 percent; p>0.05); and bitter taste (40 vs. 7 percent; p=0.003). Turning to the vardenafil study,¹⁰⁶ six persons in the vardenafil group and two persons in the placebo group experienced adverse effects, which included headache, diarrhea, nasal congestion, and priapism.

The authors of the two ginkgo biloba trials reported side effects. In the smaller study (n=60),¹¹¹ the authors noted that diarrhea occurred in 6 percent of placebo and 3 percent of treated participants, while headaches occurred in 3 percent of the persons in each group. In the larger study,⁹³ the authors reported numerous adverse effects, with the highest incidence observed for gastrointestinal effects (3.1 percent in both study groups) and the lowest for hyperacusis (0 percent in the treated group, 0.4 percent in the placebo group). Overall, the between-group differences in incidence were not statistically significant for any adverse effect in the larger trial. In the zinc trial,⁸⁶ two patients in the intervention group reported minor gastric disturbances. Similarly, two patients in the honeybee larvae RCT⁸⁵ dropped out due to ‘discomfort’ (one patient in each study group).

Table 11. Treatment emergent adverse effects reported in studies evaluating pharmacological and food supplement interventions

Pharmacological Intervention Category	Specific Intervention	Dropouts Due to AE (% of dropouts) Reason(s)	AE Info Collected	Treatment Emergent AE (did not drop out of study) Reason(s)
Antidepressant drugs	Sertraline (SSRI antidepressant) vs. placebo ^{99,122}	NR	Yes	NR
	Paroxetine (SSRI antidepressant) vs. placebo ¹¹³	22/26 (84.6%) Sexual dysfunction Tx n=17(29.8%) PI n=4 (6.9%) p=0.001 Drowsiness Tx n=11 (19.3%) PI n=2 (3.4%) p=0.007 Dry mouth Tx n=8(14.0%) PI n=1 (1.7%) p=0.015 NS results: Sweat (11), Insomnia (11), GI distress (7), Tremor (1), Headache (5)	Yes	NR
	Trazodone (SARI antidepressant) vs. placebo ⁹⁰	0	NR	Sleepiness Tx n=3 (7%) PI n=1 (2.4%)
	Nortriptyline (2 nd gen tricyclic antidepressant) vs. placebo ¹¹⁵	14/25 (56.0%) Anticholinergic side effects and sedation (11)	NR	NR

Table 11. Treatment emergent adverse effects reported in studies evaluating pharmacological and food supplement interventions (continued)

Pharmacological Intervention Category	Specific Intervention	Dropouts Eue to AE (% of dropouts) Reason(s)	AE Info Collected	Treatment Emergent AE (did not drop out of study) Reason(s)
Neurotransmitter drugs	Gabapentin(GABA analogue – GABAergic) vs. placebo ¹⁰⁹	9/20 (45.0%) Nausea n=3 Weight gain n=2 Sleep disturbance n=2 Dizziness n=1	Yes	NR
	Baclofen (selective GABAB1 receptor agonist) vs. placebo ¹¹⁹	8/11 (72.7%) All withdrew because of side effects (not specified)	Yes	Confusion Tx n=8 (26.7%) PI n=0 <0.005 Dizziness Tx n=12 (40.0%) PI n=1 (3.4%) <0.001 Drowsiness Tx n=15 (50.0%) PI n=3 (10.3%) <0.001
	Alprazolam (benzodiazepine – anxiolytic) vs. placebo ²⁸	2/4 (50%) Excessive drowsiness	Yes	Excessive drowsiness 7/17 (41%)
	Acamprosate vs. placebo ¹¹⁴	NR	NR	NR
	Acamprosate vs. placebo ⁸²	9/50 (18%) 2 in Tx group and 7 in PI group (AEs included epigastralgia, choking, depression (n=1); authors did not break down AEs by group or percentage)	Yes	Epigastralgia and choking were reported in 12% of Tx group and 20% of PI group, including 9 participants who withdrew
Other Drugs	Methylprednisolone (intratympanic injection) vs. placebo ¹¹⁷	0	NR	Pain during injection Tx: 67% PI 52% NS Burning sensation: Tx 57% PI 17% p=0.002 Vertigo Tx 57%, PI 38% NS Bitter taste Tx 40%, PI 7% p=0.003
	Deanxit + clonazepam vs. placebo + clonazepam ¹⁰⁷	NR	NR	NR
	Vardenafil (PDE5 inhibitor) vs. placebo ¹⁰⁶	5/7 (71.4%)	NR	Headache Tx n=1; PI n=2 Diarrhea Tx n=2; PI n=0 Nasal congestion Tx n=2; PI n=0 Prolonged penile erection Tx n=1; PI n=0

Table 11. Treatment emergent adverse effects reported in studies evaluating pharmacological and food supplement interventions (continued)

Pharmacological Intervention Category	Specific Intervention	Dropouts Due to AE (% of dropouts) Reason(s)	AE Info Collected	Treatment Emergent AE (did not drop out of study) Reason(s)
Food Supplements	Gingko biloba vs. placebo ¹¹¹	0	NR	Diarrhea Tx n=1 (3%) PI n=2(6%) Headache Tx n=1 (3%) PI n=1 (3%)
	Zinc vs. placebo ⁸⁶	NR	Yes	Minor gastric disturbances Tx n=2 (6%); PI n=0
	Honeybee larvae vs. hydrogenated dextrin ⁸⁵	Discomfort (term not further defined by authors) Tx n=1; Comparator n=1	Yes	Authors specifically report that no AEs occurred besides 'discomfort' (n=2) leading to drop-out
	Gingko biloba vs. placebo ⁹³	NR	Yes	Gastrointestinal Tx n=15; PI n=15 Ear pressure/blocking Tx n=10 ; PI n=4 Dizziness/nausea Tx n=6; PI n=7 Headache Tx n=4; PI n=4 Mouth ulcer/dryness/bad taste Tx n=3 ; PI n=6 Worsening sleep/dreams Tx n=4 ; PI n=3 Flushing/redness in face Tx n=1; PI n=4 Skin problems Tx n=2 ; PI n=3 Awareness of heartbeat Tx n=3 ; PI n=3 Worsening hearing Tx n=1; PI n=1 Hyperacusis Tx n=2; PI n=2 Miscellaneous Tx n=8 ; PI n=8

Abbreviations: AE = adverse effects; gen = generation; n = sample size; NR = not reported; NS = not significant; PDE5 = phosphodiesterase type 5; PI= placebo; SARI = serotonin antagonist reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; Tx = treatment; vs. = versus

Strength of Evidence—Adverse Effects

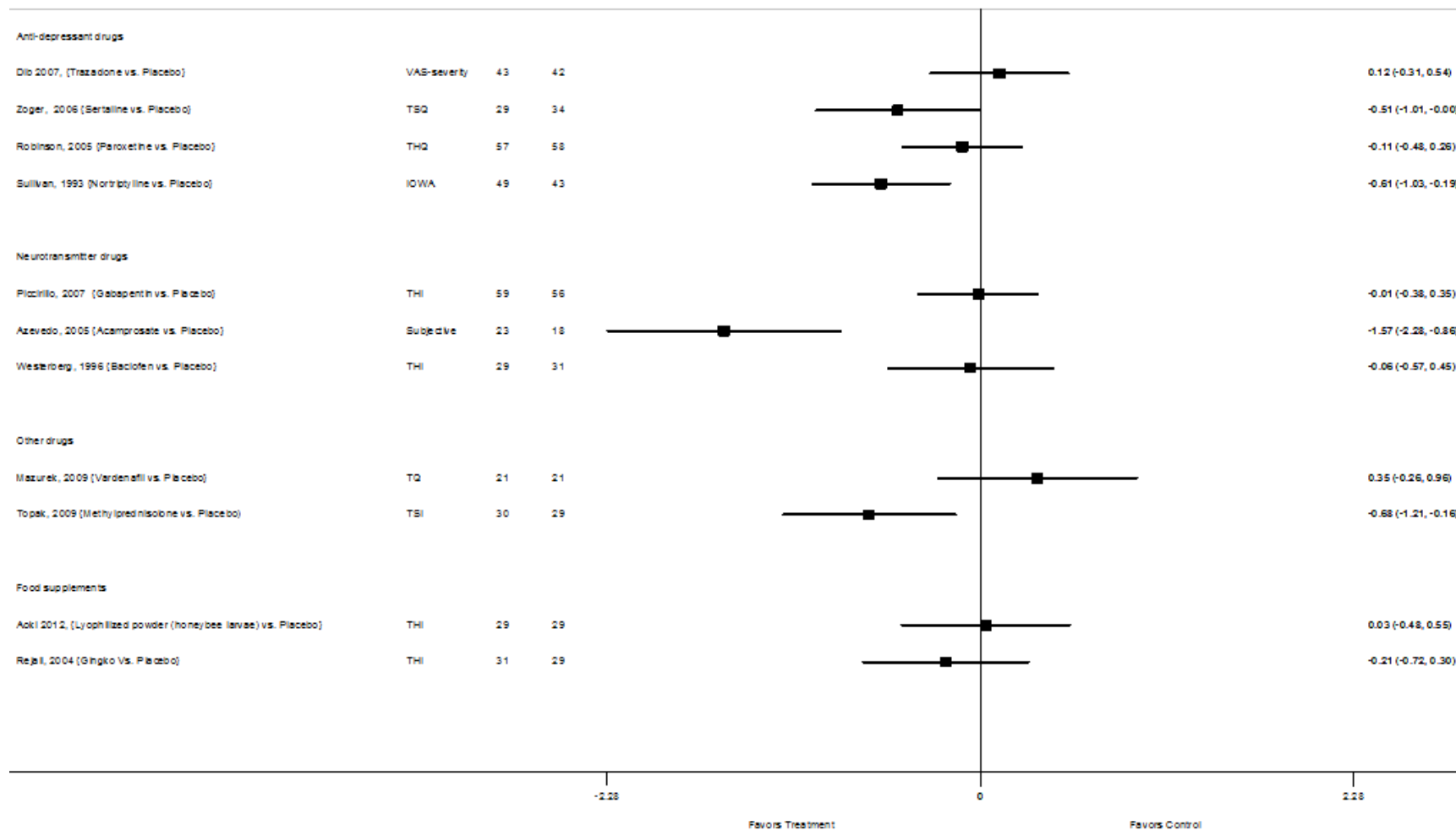
The study protocol identified surgical outcomes, sedation, and worsening symptoms as adverse effects of primary interest. There were four studies reporting symptoms of sedation (sleepiness, drowsiness) and this was reported in studies using antidepressants (trazodone and paroxetine) and neurotransmitter drugs (baclofen, alprazolam). Table 12 shows the ratings across the four domains for the adverse effect of sedation. The findings for sedation were inconsistent and deemed imprecise as estimates of affected patients were poorly characterized; the SOE for the outcome of sedation was judged to be insufficient in patients with tinnitus.

Table 12. Strength of evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report on the adverse effect of sedation

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Pharmacological Drowsiness or excessive sleepiness	Anti-depressant vs. placebo	2 ^{90,113}	Low	Inconsistent	Direct	Imprecise	N/A	Insufficient
	Neuro-transmitter Drugs (Baclofen, Alprazolam) vs. placebo	2 ^{28,119}	Low	Inconsistent	Direct	Imprecise	N/A	Insufficient

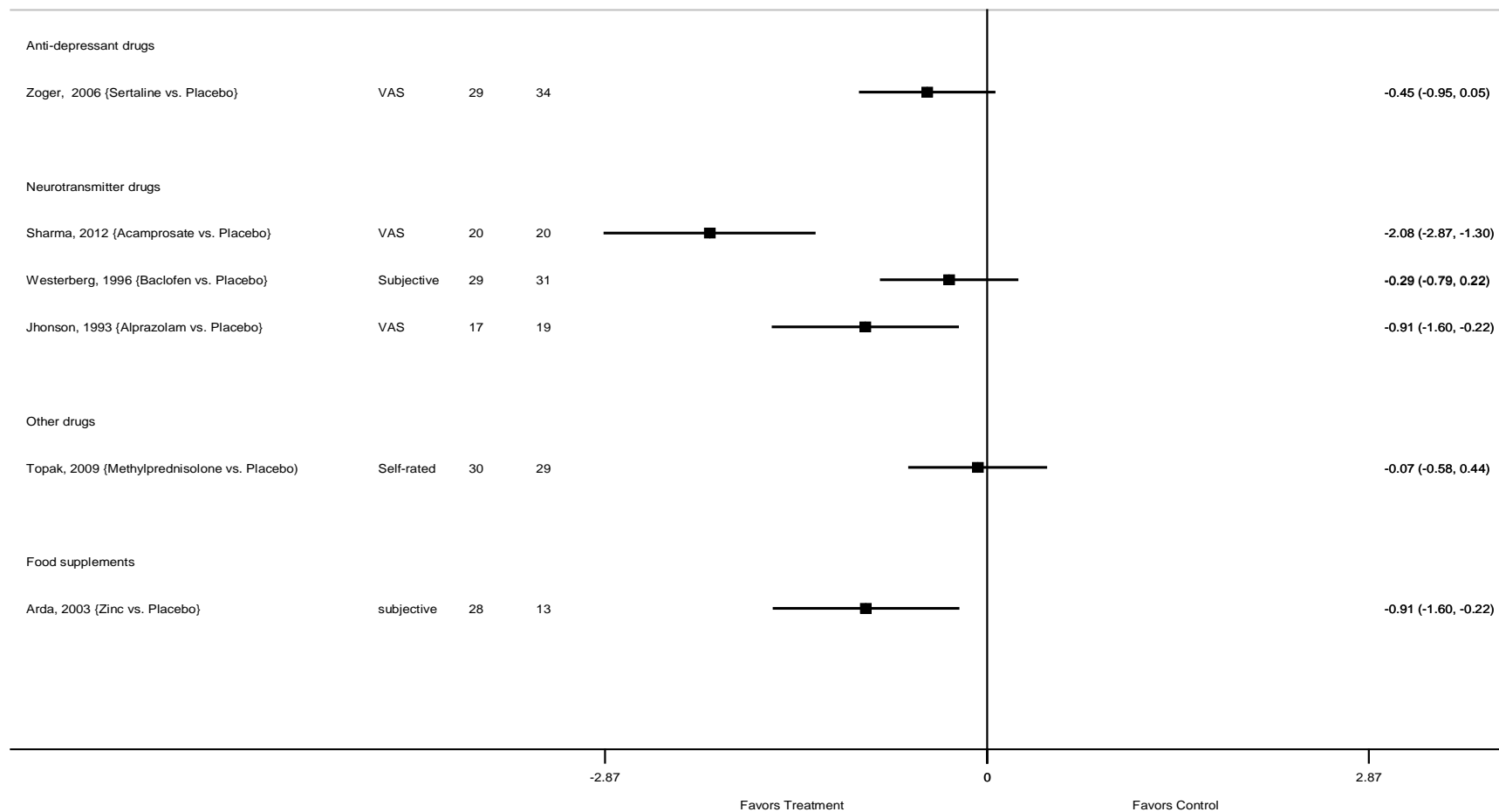
Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference

Figure 4. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report tinnitus-specific quality of life outcomes



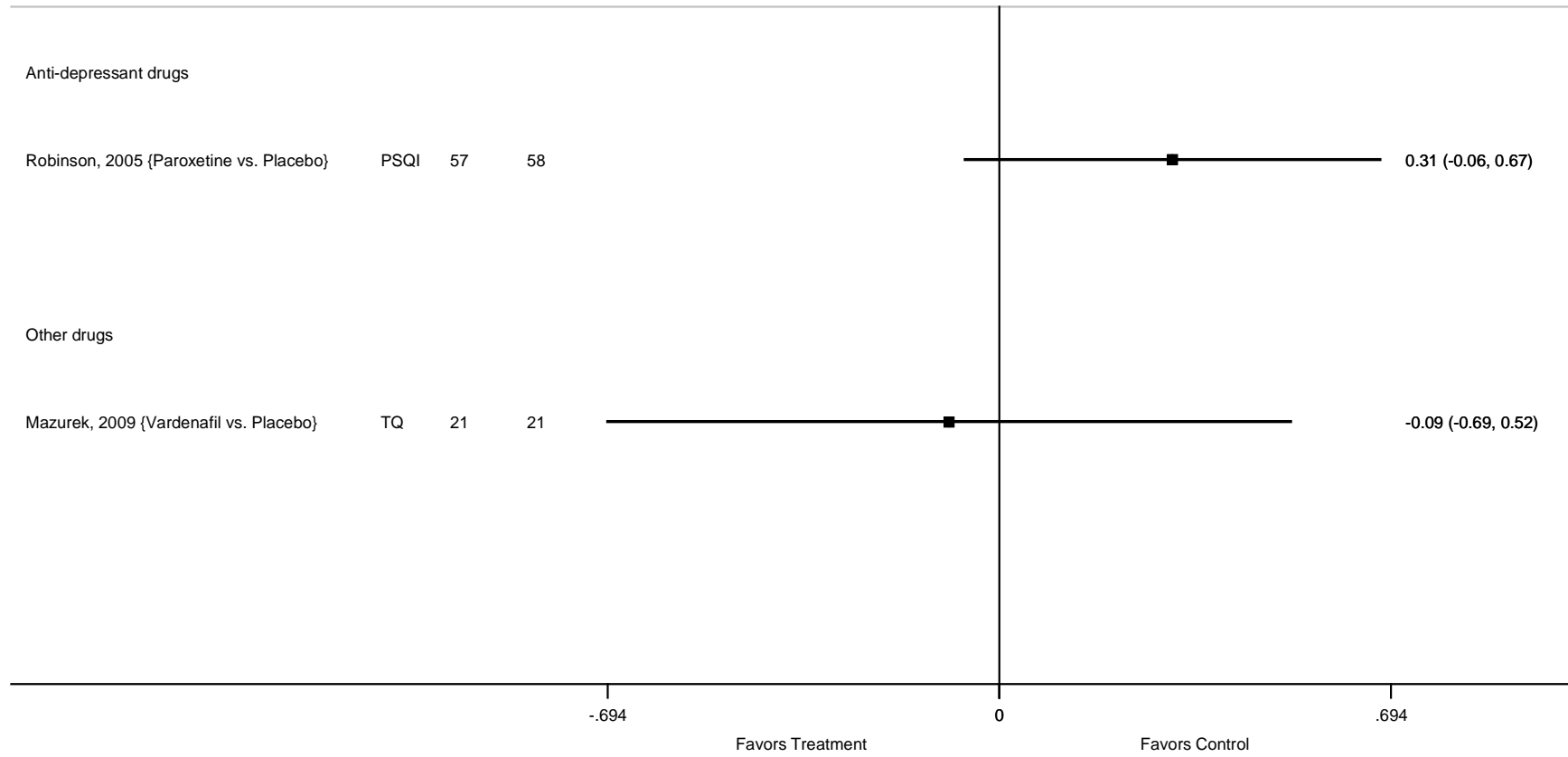
Note: A decrease in score indicates improvement.

Figure 5. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report subjective loudness outcomes



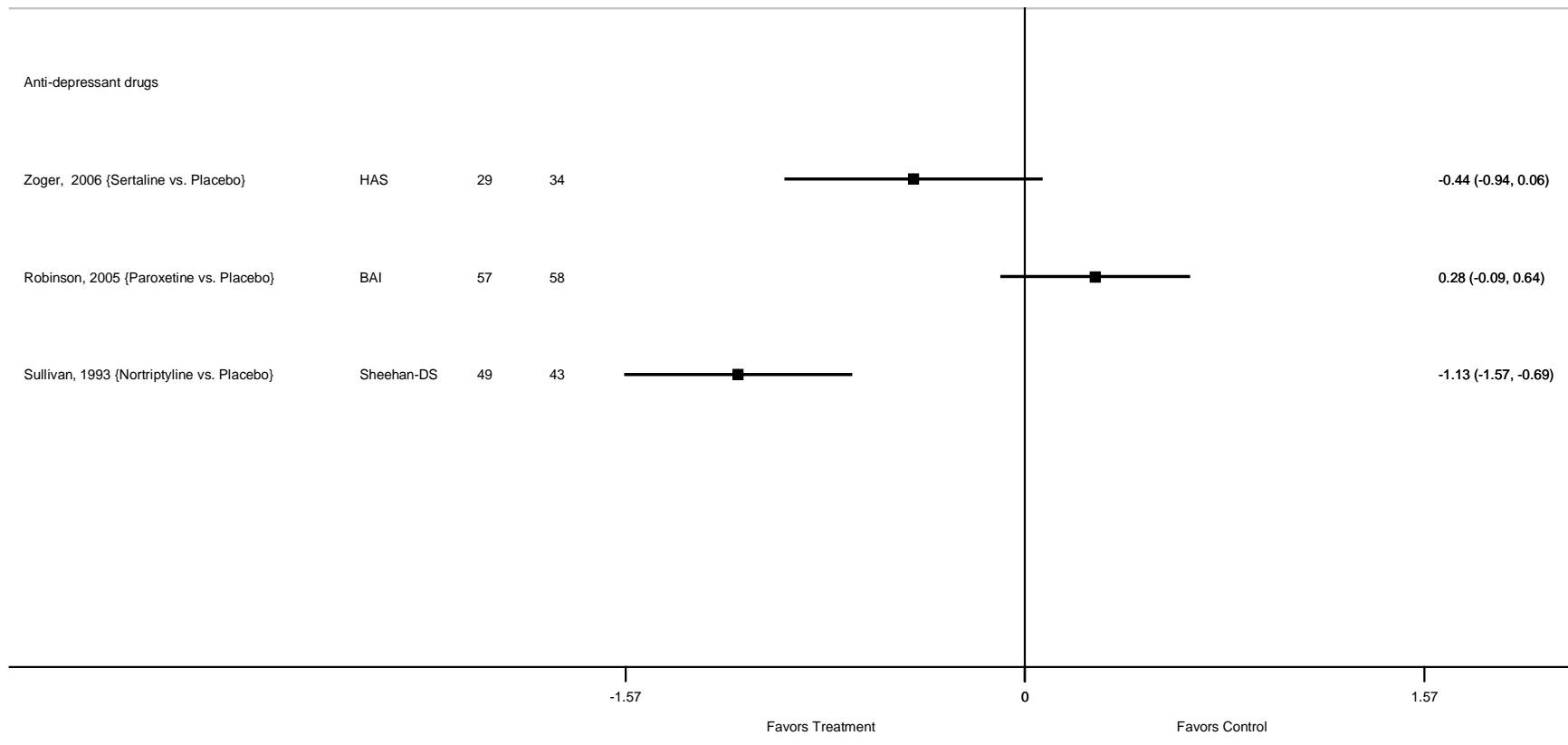
Note: A decrease in score indicates improvement.

Figure 6. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report sleep disturbances outcomes



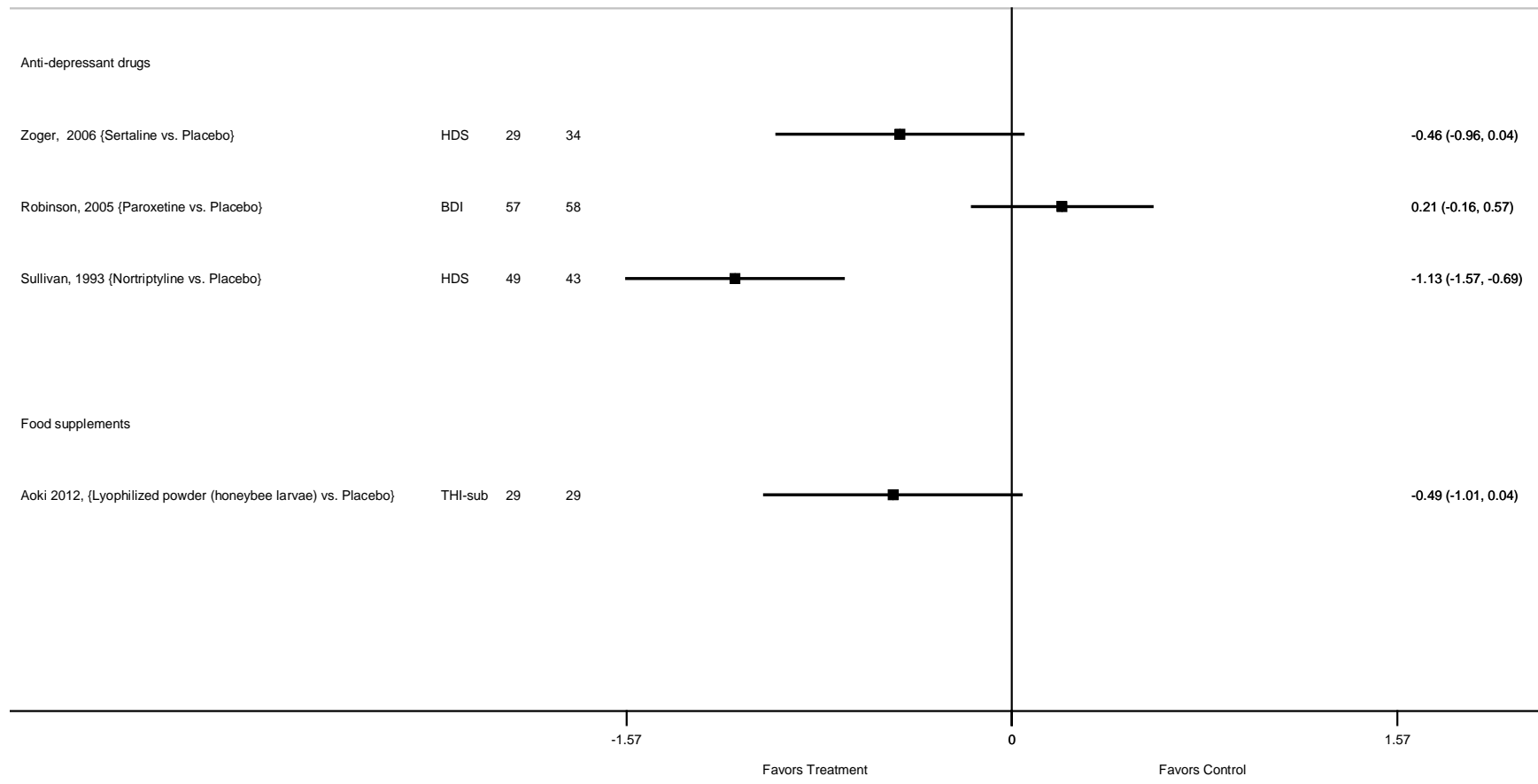
Note: A decrease in score indicates improvement.

Figure 7. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report anxiety symptom outcomes



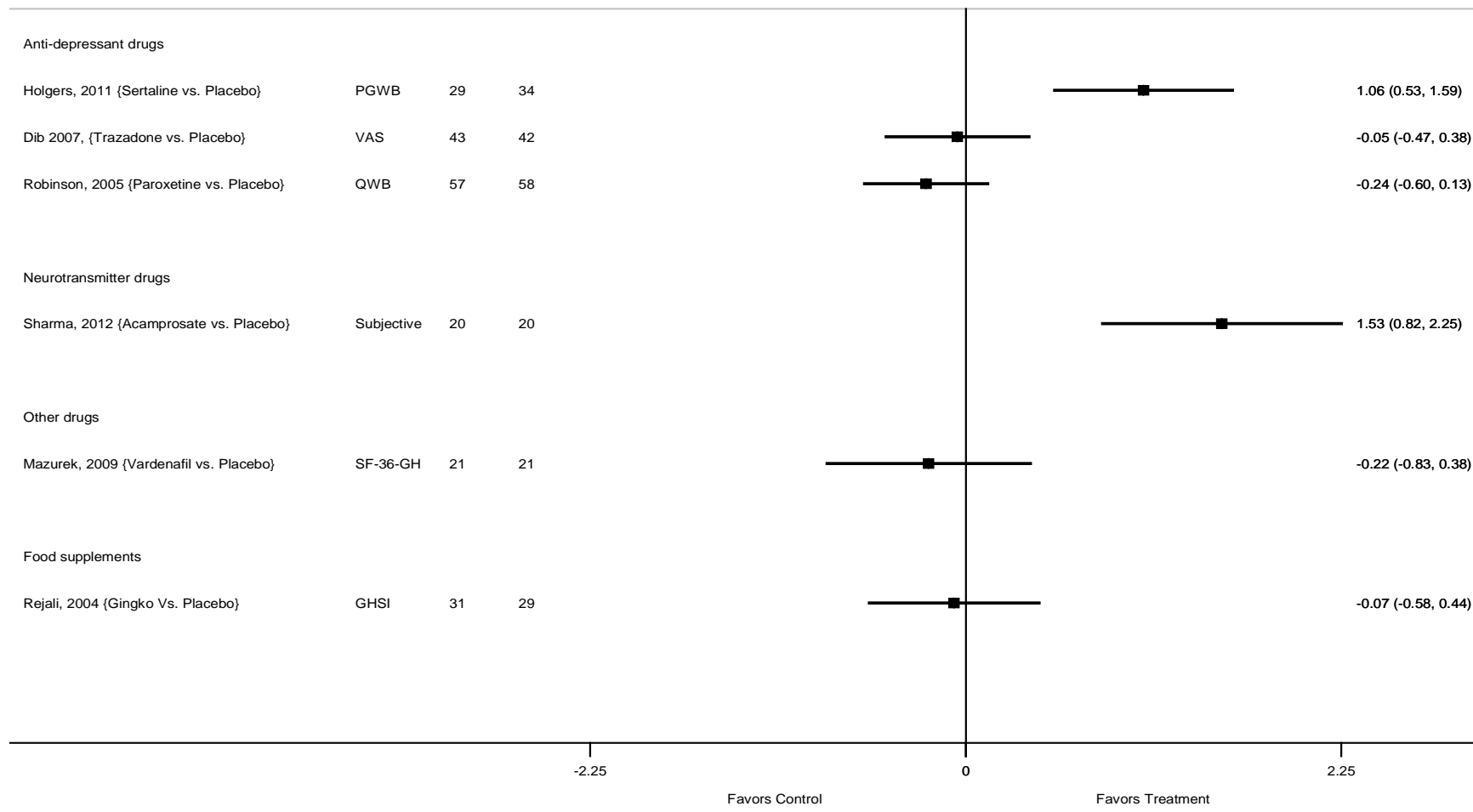
Note: A decrease in score indicates improvement.

Figure 8. Studies with inactive comparators that evaluate the pharmacological and food supplement interventions and report depression symptoms outcomes



Note: A decrease in score indicates improvement.

Figure 9. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report global quality of life outcomes



Note: A decrease in score indicates improvement.

Medical Interventions

Key Messages

Eleven studies were included for medical interventions in KQ2:^{35,83,88,89,94,103,105,108,110,116,118}

- Six evaluated Repetitive Transcranial Magnetic Stimulation (rTMS) or electromagnetic stimulation^{83,88,94,103,105,110}
- Three evaluated low level laser therapy (LLLT)^{35,89,108}
- One evaluated acupuncture¹¹⁸
- One evaluated acoustic coordinated reset neuromodulation (ACRN) therapy¹¹⁶

All the studies in the medical intervention grouping have relatively small sample sizes (less than 60 subjects total).

The risk of bias in the 11 studies evaluating medical interventions was generally fair (n=9 fair,^{35,83,89,94,103,105,108,116,118} n=1 poor,⁸⁸ n=1 good¹¹⁰).

Tinnitus-Specific Quality of Life

- This outcome was evaluated in nine studies with inactive controls using different types of instruments. The SOE was insufficient for studies evaluating rTMS (n=4) (high risk of bias, variability in dose and areas treated), and for those interventions that had single studies (high frequency pulsed electrical stimulation (n=1), LLLT (n=2) (different types of LLLT), ACRN (n=1) and acupuncture (n= 1)).

Subjective Loudness

- This outcome was evaluated in four studies. The SOE was insufficient for studies evaluating LLLT (n=2), ACRN (n=1) and acupuncture (n=1) because of high risk of bias and imprecise estimates.

Sleep Disturbance

- No studies evaluated this outcome.

Anxiety Symptoms

- A single study evaluating LLLT evaluated this outcome and the SOE was deemed insufficient.

Depression Symptoms

- A single study evaluating LLLT evaluated this outcome and the SOE was deemed insufficient.

Global Quality of Life

- No studies evaluated this outcome

Characteristics of Included Studies

Eleven studies were included for medical interventions in KQ2. Six^{83,88,94,103,105,110} of these evaluated repetitive transcranial magnetic stimulation (rTMS) or electromagnetic stimulation,

three evaluated low level laser therapy (LLLT)^{35,89,108} and one each evaluating acupuncture¹¹⁸ and acoustic coordination reset neuromodulation (ACRN) therapy.¹¹⁶ See Appendix E for the Characteristics of Included Studies Evidence Tables.

Population—Duration and Severity of Tinnitus

The subjects in the majority of studies were from the general population of those experiencing subjective idiopathic tinnitus. Two studies focused on specific sub-populations (some tinnitus presenting with sensorineural hearing loss or from Ménière's disease³⁵ or tinnitus that was treatment resistant for one year).¹¹⁸

For some studies, the duration of time participants had been bothered by their tinnitus before being eligible for the intervention study was a minimum of 3 months,^{89,105} 6 months,^{83,94,116} 1 year,¹¹⁸ or less than 5 years.¹¹⁰ Other studies did not specify a minimum threshold for duration in order to be eligible for study participation. Two studies also required subjects to be right handed^{83,88} and had symptoms that had not resolved following pharmacological interventions after 3 months⁸³ or any following any other type of treatment.⁸⁸ Other studies did not specify a time period.

The severity of the tinnitus was not consistently identified prior to treatment, but studies reported recruiting patients with tinnitus described as disturbing,¹⁰³ disabling chronic,¹⁰⁸ and chronic.¹¹⁶ Other papers enrolled patients with treatment resistant tinnitus,^{88,118} and three did not report on severity of tinnitus at enrollment.^{35,105,110} Some studies included a pre-study assessment by an otolaryngologist (ENT),^{88,89} and audiologist or audiology tests.^{83,94,103,108}

In the rTMS and electromagnetic stimulation studies, the subjects were identified as having a range of tinnitus symptom duration from 7 months to 60 years,⁹⁴ less than 5 years,¹¹⁰ and 6 months to 20 years.⁸⁸ One study provided only mean duration of tinnitus (11.7 and 10.7 years).¹⁰³ Two studies did not report duration of symptoms of included subjects.^{83,105}

The study evaluating ACRN¹¹⁶ did not report any information regarding duration of tinnitus. In the LLLT studies, subjects were identified as having a range of duration of tinnitus symptoms from 3 months to 25/26 years^{35,108} and 6 months to 45 years.⁸⁹ The acupuncture study¹¹⁸ reported only the average duration (from 7.4 and 9.4 years).

Interventions and Role of Device Manufacturers

Repetitive Transcranial Magnetic Stimulation (rTMS) and Electromagnetic Stimulation

Five studies focused on rTMS^{83,88,103,105,110} and one on high-frequency pulsed electromagnetic energy.⁹⁴ Table 13 shows the specifics of the rTMS and electromagnetic stimulation devices, dose and placement on the head. One study⁹⁴ appears to use a markedly different approach to electromagnetic stimulation and is not classified as rTMS. The five studies evaluating the use of rTMS appeared to stimulate the cortex most commonly associated with auditory function and only two studies^{83,103} used additional devices (stereotaxy and MRI) to locate the cortical areas of interest. The electromagnetic stimulation parameters markedly varied with respect to number of session (5 sessions over two weeks)⁸³ to 20 consecutive sessions over 4 weeks.¹¹⁰ Similarly, the dose of electromagnetic stimulation varied across studies from 1,500 stimulations at 1 Hz⁸³ to 900 bursts at 5 Hz.¹¹⁰

Table 13. Details of the devices, dose and placement of rTMS and electromagnetic stimulation interventions

Study	Device	Dose and Duration	Information About the Location and Method of Treatment Application as Specified Within the Studies
Ghossaini, ⁹⁴ 2004	Device: Diapulse (model D103); Diapulse Corporation of America	Electromagnetic energy group: High-Frequency Pulsed Electromagnetic Energy (Diapulse) set to produce pulsed electromagnetic energy at 27.12 MHz in 65 μ s burst with repetition of 600 pulses per second at 975 W peak. Patients received 30-minute treatments with the Diapulse device (model D103) 3 times per wk for 1 month. Sham rTMS group: deactivated machine but same protocol.	Treatment was accomplished by placing the center of the head of the Diapulse unit approximately 1 inch lateral to the auricle. Treatment was placed only on one side of the skull. Patients with bilateral tinnitus received treatment to the ear with louder tinnitus.
Anders, ⁸³ 2010	Device: Magstim SuperRapid; (The Magstim Company Ltd., Whitland, UK). Coil: Figure-eight-shaped coil	rTMS 1500 stimulations per session occurring over 2 intervals within a session at 1 Hz. In total 5 sessions over 2 weeks. Sham rTMS: coil was tilted 45 degrees away from skull with only one wing touching the skull.	Navigation of the coil on the surface of the skull Frameless neuro-navigation system (Magstim Co. Ltd, Whitland, UK) over the auditory cortex (Brodmann area 41 and 42) according to individual structural MRI data (T1 weighted 1.5 system Gyroscan NT, Phillips, Medical Systems, Shelton CT). Coil was positioned over the primary auditory cortex marked by water resistant pen during stereotaxy navigation session.
Marcondes, ¹⁰⁵ 2010	Device: Dantec Stimulator (Medtronic, Minneapolis, MN, USA) Coil: Figure 8 coil 7 cm	rTMS group: 17 minutes at 110% intensity if motor threshold (1020 stimuli) at a frequency of 1 Hz. Treatment administered for 5 consecutive days.. Sham rTMS group: Performed with the sham coil system.	Applied over the left temporoparietal cortex in accordance with previous studies. Coil was centered at the midline between the electroencephalographic electrode positions T3 and P3 with the handle of the coil angled backward of about 45 degrees away from the midline TMS. All subjects were given earplugs.
Chung, ⁸⁸ 2012	Device: Magstim SuperRapid; (The Magstim Company Ltd., Whitland, UK). Coil: Figure-eight-shaped coil	rTMS group: -Intensity setting at 80% of the resting motor threshold (RMT) as per previous methods. Continuous theta-burst rTMS (cTBS) was delivered at a burst frequency of 5 Hz (the theta rhythm in the EEG); each burst consisted of 3 pulses repeated at 50 Hz. 900 pulses (300 bursts) of stimulation once daily for 10 consecutive business days. Sham group: Received an identical protocol to the active-stimulation group, but with the sham coil tilted away from the skull.	Coil was placed over the auditory cortex (temporoparietal lobes): the distance between electrodes on the scalp and cortex is calculated on average as 23.8 mm.

Table 13. Details of the devices, dose and placement of rTMS and electromagnetic stimulation interventions (continued)

Study	Device	Dose and Duration	Information About the Location and Method of Treatment Application as Specified Within the Studies
Plewnia, ¹¹⁰ 2012	Device: Magstim SuperRapid; (The Magstim Company Ltd., Whitland, UK). Coil: Figure-eight-shaped coil (diameter of each winding 70 mm, biphasic stimuli of 250 us)	rTMS group. Continuous theta burst stimulation (cTBS) which was standardized to 80% individual active motor threshold. cTBS was applied to each hemisphere in alternating order. Each stimulation train (40s) consisted of 600 stimuli applied in burst of 3 pulses at 50 Hz given every 200 msec (i.e., 5 Hz). Fifteen minutes after the first 2 trains, a second pair of cTBS trains was given (a total of 2,400 stimuli per day). Applying a second train 15 minutes later has previously been shown to prolong the inhibitory effects. Patients received daily cTBS for 4 weeks (20 sessions). Sham group: for adequate masking of the patients, sham stimulation was performed as per cTBS but behind the mastoid.	Because the primary auditory cortex cannot be reached adequately by rTMS and in order to compare the effects of cTBS to secondary and higher order processing areas, the 10–20 EEG electrode placement system was used to localize. Temporal cortex (Brodmann area 39 (TAC: halfway between T5/P3 and T6/P4)) and Temporoparietal cortex (Brodmann area 42/22 [SAC: halfway between T3/C3 and T4/C4]). Sham (behind the mastoid) The coil was hand-held during stimulation trains to allow for optimal fixation. All patients were seated in a comfortable chair while they were receiving 4 x 40 s of cTBS. There was no other input to or activity of the patients during stimulation. Disposable earplugs (ColorPlux®; noise reduction rating 35 decibels) were used while cTBS was applied.
Langguth, ¹⁰³ 2008	Medtronic (90 mm outer diameter, Medtronic, Minneapolis, MN, USA) Figure 8 coil	The study aimed to investigate whether priming stimulation enhances the efficacy of low-frequency rTMS Intervention: Priming protocol (960 stimuli; 6 Hz) preceded rTMS (1,040 stimuli; 1 Hz and an intensity of 90% motor threshold (16 trains lasting 10 s separated by 20 s). Stimulation was provided over 10 consecutive days. Comparator: standard protocol rTMS: (2,000 stimuli; 1 Hz and 110% motor threshold)	A neuronavigational system (Brainvision, Brainlab) based on frameless stereotaxy and adapted for magnetic stimulation allowed for navigation of the coil on the surface of the skull over the auditory cortex according to the individual MRI data. The handle of the coil was pointing upwards. Treatment over the left auditory cortex (independent of right or left handedness).

Abbreviations: cm = centimeter; cTBS = continuous theta burst stimulation; EEG = electroencephalogram; Hz = Hertz; Mhz = megahertz; Mnth = month; MRI = Magnetic resonance imaging RMT = registered massage therapist rTMS = repetitive transcranial magnetic stimulation; SAC = secondary auditory cortex; TAC = temporoparietal association cortex; TMS = Transcranial magnetic stimulation; wk = week

Acoustic Coordinated Reset Neuromodulation

One study¹¹⁶ evaluated the use of acoustic coordinated reset neuromodulation (ACRN). As described by the study authors, “the concept of ACRN comprises a spatial and temporal coordination of the applied stimuli to induce desynchronization leading to anti-kindling” and is applied to the primary auditory cortex, where short sinusoidal tones of different frequencies (f1 to f4) induce a soft reset in different target areas grouped around the tinnitus focus. Three ACRN cycles, each comprising a randomized sequence of four tones, are followed by two silent cycles.

That pattern is repeated periodically. The random variation of the tone sequences and the 3:2 “on and off” pattern optimizes the desynchronizing ACRN effect.

In this study, four different stimulation groups and one placebo group were evaluated. Groups 1, 3, and 4 (G1, G3, G4) used four tones grouped around the tinnitus frequency for each patient (ft); G3 differed only in repetition rate being adapted to the individual EEG (i.e., band peak). For group 2 (G2) each ACRN cycle was formed by a varying composition of four tones chosen out of twelve tones from the surrounding frequencies. Placebo stimulation or group 5 (G5) was formed similar to G1 using a down-shifted stimulation-frequency (fp) ($fp=0.7071 \cdot ft / (2n)$, fp within (300 Hz, 600 Hz)) outside the synchronized tinnitus focus. Note that a readjustment of stimulation parameters could be undertaken if the matched tinnitus frequency had changed relative to baseline.

Treatment in G1, G2, and G3 was applied for 4 to 6 hours per day and applied continuously or split into several sessions not less than 1 hour. In contrast, G4 and G5 received stimulation for only 1 hour daily. Patients were stimulated for 12 weeks using portable acoustic device and comfortable earphones; this 3 month treatment was followed by an additional off stimulation period of 4 weeks and an optional 24 week off-label extension period. Although not specified, it is likely that the stimulation was administered by the patient (as the device was portable) but it is not clear what role if any the neurologist had in administering the treatment (but EEG was used to optimize the frequencies selected for individual patients and thus specialized professional expertise was required in the initial assessment of tinnitus frequency for the purposes of selecting the characteristics of the acoustic stimulation). 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.

Low Level Laser Treatment

Two studies reviewed the effects of low level laser treatment (LLLT)^{35,108} relative to sham laser and one study used LLLT in combination with counseling relative to sham LLLT and counseling.⁸⁹ Note that the role of the manufacturers of the LLLT devices was not specified in the studies; similarly, potential conflict of interest by the study authors with regards to payment from the manufacturer was not reported in any of these three studies.

One study¹⁰⁸ used gallium-aluminium-arsenide (Ga-Al-As) diode laser (Uni-laser 301P, type 301.000, 3B) with a maximum output power of 140 mW and a wavelength of 830 nm with invisible radiation (probe beam 670 nm with less than 1mW output power); the frequency spectrum for the laser was in the range of 10–1500 Hz. The tip of the laser probe was inserted in the external acoustic meatus, pointing the beam towards the tympanic membrane and the promontory of the affected ear. Each of the 15 treatment settings lasted 10 min. Power of 50 mW with a continuous wave resulted in a total application of 30 J in each session. Only one ear was treated even if the subject had bilateral tinnitus. Although not explicitly, stated it is likely that the laser was administered by a technician in a clinical setting.

Two studies^{35,89} used a similar laser device (see website for this device: www.tinnitool.com/en/therapie_moeglichkeiten/index.php) where the patient administered the laser using a headset or ear attachment to ensure consistency in the administration of the laser. One study³⁵ used the TinniTool (Adisma[®]) and a second study⁸⁹ used the LLLT (TinniTool EarLaser, DisMark GmbH, Maur, Switzerland) which may be very similar devices. These devices are diode lasers with a wavelength of 650 nm and absolute power output of 5 mW with a continuous wave. One study³⁵ describes the laser probe inserted into a special fixation material in a specifically designed headset to facilitate positioning in the auditory meatus; the laser beam is

projected onto the tympanic membrane through a 17-degree diverging lens, creating a spot size of 1 cm. Duration of irradiation was 20 min a day resulting in an energy density of about 6 J at the tympanic membrane; the treatment lasted 3 months. All subjects had unilateral tinnitus and although not reported in the study, it is assumed that only one ear was treated. Note that the laser was administered by the patient at their home. The second study⁸⁹ using the TinniTool EarLaser, describes the system as one composed of a laser probe that was placed at the entrance of the external auditory canal, from where the laser ray was directed toward the eardrum. The laser probe was to be used with a wearable ear hook. Patients were trained to use the device for 20 minutes per day, for 3 months. In this study, although the largest proportion of subjects had bilateral tinnitus (63 percent), it is not clear if the study subjects were instructed to treat both ears.

This second study⁸⁹ using the TinniTool EarLaser also combined counseling (10 sessions of 40 minutes, distributed over the 3 month treatment period) with both the active LLLT and the sham LLLT groups. The counseling intervention included a multi-modal approach and combined tinnitus retraining therapy principles and psychosomatic approaches (both hypnotic and relaxation techniques) over the 10 sessions.

Acupuncture

One study reviewed the effects of Chinese acupuncture relative to sham acupuncture.¹¹⁸ Treatments were given over 2 months where subjects received three blocks of treatments (10, 5, and 10, separated by 1 week) for a total of 25 sessions. The treatment was administered daily for 30 minutes. All subjects were treated over five different points (SI -19, G 2, SJ 17, SJ 19, DU 20); however, distal points and the “methods of manipulation” varied with individual patients. Bilateral treatment was administered irrespective of whether the patient suffered with unilateral or bilateral tinnitus. A non-penetrating Japanese acupuncture needle was used as the sham acupuncture. The sham needles were inserted superficially into the skin over random non-acupuncture sites for 30 minutes.

Comparators

Table 14 shows the types of comparators included in the studies. Description of the sham interventions are described in the interventions section.

Table 14. Interventions and comparators used in studies that evaluate medical interventions and outcomes

Medical Intervention	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects	
RTMS	INACTIVE COMPARATOR								
	1 rTMS vs. sham Anders, ⁸³ 2012						THI ⁻ , TQ-modified, VAS	Yes	
	2 rTMS vs. sham Marcondes, ¹⁰⁵ 2010						THI	None	
	3 rTMS vs. sham, Chung, ⁸⁸ 2012				VAS		THI ⁻ TQ	None	
	4 rTMS (cTBS) secondary auditory cortex vs. sham, Plewnia, ¹¹⁰ 2012						TQ	Yes	
	rTMS (cTBS) temporoparietal cortex vs. sham, Plewnia, ¹¹⁰ 2012						TQ	Yes	
	5 High-Frequency Pulsed Electromagnetic Energy vs. sham Ghossaini, ⁹⁴ 2004						THI ⁻ , TMR	Yes	
	HEAD-TO-HEAD								
	1 rTMS Standard protocol (2000 stimuli; 1 Hz) vs. rTMS Priming protocol (960 stimuli; 6 Hz+1040 stimuli;1 Hz) Langguth, ¹⁰³ 2007							TQ	None
	2 rTMS (cTBS) secondary auditory cortex vs. rTMS (cTBS) temporoparietal cortex, Plewnia, ¹¹⁰ 2012							TQ	Yes
Acupuncture	INACTIVE COMPARATOR								
1 Acupuncture vs. sham Vilholm, ¹¹⁸ 1998					VAS		VAS-Ann ⁻ , VAS-Awr	NR	
Laser	INACTIVE COMPARATOR								
	1 Laser Therapy vs. sham Mirz, ¹⁰⁸ 1999		STAI	BDI	VAS		THI ⁻ , VAS-Ann, VAS-Att	None	
	2 Laser Therapy vs. sham Teggi, ³⁵ 2009				VAS		THI	Yes	
	HEAD-TO-HEAD								
1 Experimental (LLS+): low level laser + counseling Control (LLS-): same counseling as LLS+ plus faked stimulation device Cuda, ⁸⁹ 2008							THI	NR	

Table 14. Interventions and comparators used in studies that evaluate medical interventions and outcomes (continued)

Medical Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse effects
Neuromodulation		INACTIVE COMPARATOR							
	1	ACRN G1 vs. placebo Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G2 vs. placebo Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G3 vs. placebo Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G4 vs. placebo Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		Head-to-head							
	1	ACRN G1 vs. G2, Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G2 vs. G3, Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G3 vs. G4, Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G1 vs. G3, Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G1 vs. G4, Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes
		ACRN G2 vs. G4, Tass, ¹¹⁶ 2012				VAS		TQ [*] VAS	Yes

Abbreviations: ACRN = acoustic coordinated reset neuromodulation; Ann = annoyance; Att = attention; Awr = awareness; BDI = Beck Depression Inventory; cTBS = continuous Theta Burst Stimulation; G(1, 2, 3, 4) = group (1, 2, 3, 4); Hz = hertz; LLS = low level laser; NR = not reported; QoL = quality of life; rTMS = repetitive transcranial magnetic stimulation; STAI = State-Trait Anxiety Inventory; THI = Tinnitus Handicap Inventory; TMR = Tinnitus Magnitude Rating; TQ = Tinnitus Questionnaire; VAS = visual analogue scale; vs. = versus

*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Outcomes

Most studies reported data on more than one outcome (Table 14, and Appendix E, Table E2.). The outcome measurement instruments used varied for the same outcomes (Table 15). For example, nine different instruments were used to measure the outcome of severity of tinnitus.

Table 15. Outcome measurements used in medical intervention studies

Outcome	Outcome Measurement Used
Tinnitus-specific QoL	THI (Tinnitus Handicap Inventory) ^{35,83,88,89,94,105,108} TQ (Tinnitus Questionnaire) ^{83,88,103,110,116} VAS (Visual Analogue Scale) ^{83,108,116,118} TMR (Tinnitus Magnitude Rating) ⁹⁴
Sleep Disturbance	No study evaluated this outcome
Anxiety Symptoms	STAI (State-Trait Anxiety Inventory) ¹⁰⁸
Depression Symptoms	BDI (Beck Depression Inventory) ¹⁰⁸
Subjective loudness	VAS (Visual Analogue Scale) ^{35,88,108,116,118}
Global Quality of Life	No study evaluated this outcome

Setting

The research settings were in departments of Otolaryngology/Otorhinolaryngology,^{83,89,105,108} Audiology,¹¹⁸ Otorhinolaryngology and Psychiatry,¹¹⁰ Psychiatry,¹⁰³ and Ear, nose and throat.³⁵ Other settings included tinnitus clinics¹¹⁶ and a university medical hospital.⁸⁸ One paper did not report on the research setting.⁹⁴

Country

The studies were carried out in seven different countries: the United States;⁹⁴ China;⁸⁸ Germany;^{103,110,116} Denmark;^{108,118} Italy;^{35,89} Spain;¹⁰⁵ and the Czech Republic.⁸³ See Appendix E, Table E2.

Sources of Funding

Sources of funding were not reported in six studies.^{35,89,105,108,110,118} One study reported industry funding,¹¹⁶ and one received a loan of the equipment being tested.⁹⁴ The remaining studies received funding from research councils, foundations, and government departments and non-profit associations.^{83,88,103}

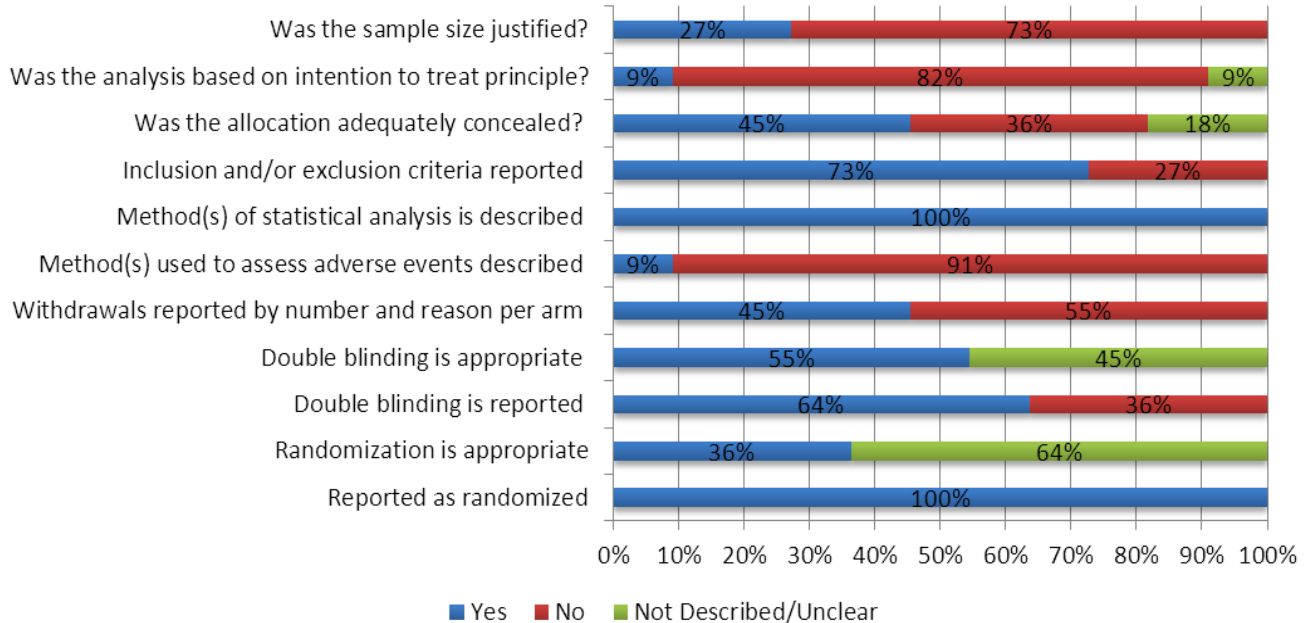
Risk of Bias for Medical Interventions

The risk of bias in the 11 studies evaluating medical interventions was generally fair risk of bias (n=9 fair,^{35,83,89,94,103,105,108,116,118} n=1 poor,⁸⁸ n=1 good¹¹⁰). All authors reported their studies as randomized, with appropriate randomization in 36 percent (n= 4) of articles.^{35,103,110,116} Method of randomization was not described in seven papers (64%).^{83,88,89,94,105,108,118} Some articles reported using double-blinding techniques,^{35,83,89,94,105,108,118} and in all but one case¹¹⁸ it was deemed appropriate. Seventy three percent of articles (n=8) reported the inclusion/exclusion criteria,^{83,88,89,103,105,110,116,118} and all described the statistical methods used (Figure 10).

Issues with risk of bias in the RCTs included a lack of reporting on withdrawals (n=6, 55%),^{88,94,105,108,116,118} no description of methods to assess adverse effects (n=4, 36%),^{88,103,116,118}

inadequate concealment of allocation (n=10, 91%),^{35,83,88,89,94,103,105,108,116,118} analysis not based on intention-to-treat principle (n=9, 82%),^{35,83,88,94,103,105,108,116,118} and inadequate justification of sample size (n=8, 73%).^{35,83,88,89,94,105,108,118}

Figure 10. Proportion of medical intervention studies achieving criteria for risk of bias



Results for Medical Interventions by Outcome

Tinnitus-Specific Quality of Life

Repeated Transcranial Magnetic Stimulation (rTMS)

Figure 11 shows the studies evaluating rTMS^{83,88,105,110} or electromagnetic stimulation⁹⁴ relative to an inactive control (see also Table 14). Most of these studies used the TQ or the THQ to evaluate tinnitus-specific QoL. Two studies^{83,105} at high risk of bias investigated low frequency (1 Hz) rTMS relative to sham stimulation and measured the outcome using the THI. Although the dose of rTMS differed (5 sessions over 2 weeks and 5 consecutive days), the changes immediately following treatment showed no significant benefit relative to sham rTMS. However, both studies seemed to report that a time effect was present. There was some worsening of symptoms at week 6 (relative to week 2) on the THI.⁸³ There were statistically significant reductions relative to baseline in the active treatment groups at 26 weeks⁸³ and 6 months.¹⁰⁵ However, active treatment appeared not to confer any further reductions in score after 6 weeks⁸³ or at 1 month.¹⁰⁵ In both studies, the groups receiving placebo stimulation did not experience statistically significant changes in THI scores over the course of followup. It is noteworthy that one of these studies¹⁰⁵ selected subjects with lower THI scores at baseline relative to other studies, suggesting that they had less severe tinnitus.

Two studies^{88,110} investigated higher frequency (5 Hz) rTMS relative to sham stimulation and measured the outcome using the THI. One of these studies⁸⁸ was at high risk of bias, and administered treatment for 10 consecutive days. Significant differences on TQ and THI scores

showed at 1 week post treatment ($p < 0.01$), but not at 1 month. The second study¹¹⁰ was at low risk of bias, and administered treatment for 20 consecutive days but showed no significant differences between treatment and sham groups immediately post treatment using the THI; this study also showed no differences at 2, 4 and 12 weeks post treatment.

One study⁹⁴ at high risk of bias examined high-frequency (27.2 MHz) electromagnetic energy using the THI as the outcome measure. The high frequency study⁹⁴ failed to detect any differences between groups. The shape of the electromagnetic stimulator appears to be encased in a round head; all other studies in this group used a figure eight coil; it is not clear how the properties of generating an electromagnetic field differ as a result of the different shaped stimulator.

Acoustic Coordination Reset Neuromodulation

The single study evaluating ACRN interventions demonstrated improvement on the Tinnitus Questionnaire (TQ) scores in all treatment groups (G1 to G4) and statistical differences relative to baseline were shown in these groups but not in placebo (G5).¹¹⁶ However, none showed a significant effect favoring treatment relative to placebo (Figure 11). VAS scores for annoyance were statistically significant and favoring treatment at 12 weeks for the G1 vs. G5 groups only.

Laser

Two studies at high risk of bias^{35,108} evaluated LLLT compared to an inactive control, and one study⁸⁹ comparing LLLT plus counseling to sham LLLT and counseling (also at high risk of bias). All of these three studies measured Tinnitus-specific quality of life using the THI.^{89,108,118} All studies showed no statistical differences between the treatment and comparator groups using the THI. It is noteworthy that one study¹⁰⁸ used a markedly different form of LLLT relative to the other two studies^{35,89} which used a self-administered applied for a minimum of 3 months. One study¹⁰⁸ evaluated 100 mm VAS for annoyance and found no between-group differences ($p=0.81$). Similarly, a VAS for attention to symptoms was evaluated and showed no statistical differences 1 month post treatment ($p=0.52$).

Acupuncture

A single trial¹¹⁸ compared traditional Chinese acupuncture to sham acupuncture over 2 months of treatment and evaluated up to 4 months of followup. Results on an unspecified VAS were not statistically significantly different at the 5 percent level for either annoyance or awareness (no p-values reported in trial publication). This trial was at high risk of bias and had only 54 subjects in total included in the study. Adverse effects were not systematically evaluated and none were reported.

Strength of Evidence—Tinnitus-Specific Quality of Life

There is insufficient evidence (four studies, 147 participants) that rTMS improves TSQoL when compared with sham treatment for idiopathic tinnitus immediately post treatment or after short term followup. The sample sizes were small (less than 30 per group), power calculations were not undertaken, and the effect estimates had wide confidence intervals; all these factors contributed to the rating of imprecision. The direction of effect was judged to be inconsistent across studies; high frequency rTMS studies^{88,110} showed differing directions of effect (statistically significant differences favoring treatment or no difference between groups) and low frequency rTMS studies^{83,105} favoring treatment but were not statistically significant. With respect to the magnitude of the treatment effects, studies were inconsistent in that effect sizes

varied from small to large (0.02 to -1.23). With respect to risk of bias, the studies were categorized as high risk of bias and only one study¹¹⁰ achieved a score greater than 7 from 12. No dose response pattern was observed; there was a trend that longer term effects (improvement in THI scores) occurred with low frequency rTMS (1 Hz) up to 6 months followup. Risk of publication bias is high given the small sample sizes of the studies. The SOE for rTMS alone for the outcome of TSQoL is rated as insufficient as the criteria for more than three of the domains were not met (Table 16).

For LLLT studies, there is insufficient evidence (two studies, 95 participants) that TSQoL improves when compared with sham treatment for idiopathic tinnitus immediately post treatment or after short term followup. Both studies were rated as high risk of bias. One study showed no difference between groups and the other favored control but was not statistically significant; the effect sizes varied from small to moderate (-0.0 to 0.33) and were deemed inconsistent (Table 16). Although the confidence intervals overlapped substantially, the small sample sizes (less than 30 per group), and lack of power calculations were factors that led to a rating of imprecise. Additionally, the types of LLLT (frequency and treatment intensity and duration) can be considered to be very different types of laser energy administration. Risk of publication bias is high given the small sample sizes of the study and limited to single publications. There is insufficient evidence for LLLT affecting TSQoL, as the criteria for more than three domains were not met.

There is insufficient evidence that high frequency electromagnetic stimulation, ACRN, or acupuncture interventions, improve TSQoL relative to inactive controls. All of these studies were at high risk of bias, had unknown consistency, and small sample sizes (less than 30 per group). Risk of publication bias is high for these interventions represented in a single study. The SOE was judged as insufficient for these interventions, as three or more of the criteria for domains were not met.

Table 16. Strength of evidence by medical interventions in the treatment of tinnitus for the outcome of tinnitus-specific quality of life in studies with inactive comparators

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
rTMS vs. sham	N/A	4 ^{83,88,105,110}	High	Inconsistent	Direct	Imprecise	-1.23 (-2.16,-0.30) to -0.02 (-0.67, 0.72)	Insufficient
Hi-frequency electromagnetic energy vs. sham	N/A	1 ⁹⁴	High	Unknown	Direct	Imprecise	-0.13 (-0.86, 0.60)	Insufficient
ACRN vs. sham	N/A	1 ¹¹⁶	High	Unknown	Direct	Imprecise	-0.50 (-1.56, 0.56) to -0.03 (-1.07, 1.02)	Insufficient
Laser therapy vs. sham	N/A	2 ^{35,108}	High	Inconsistent	Direct	Imprecise	-0.00 (-0.54, 0.53) to 0.33 (-0.29, 0.94)	Insufficient
Acupuncture vs. placebo	N/A	1 ¹¹⁸	High	Unknown	Direct	Imprecise	-0.10 (-0.63, 0.10)	Insufficient

Abbreviations: ACRN = acoustic coordinated reset neuromodulation; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; WLC = wait list control

Subjective Loudness

Four studies with high risk of bias,^{35,108,116,118} (summary risk of bias score did not exceed 7 from 12) examined loudness as an outcome in persons given medical interventions including LLLT, ACRN, and acupuncture (Table 15). Figure 12 shows the standardized mean difference for the studies that measured this outcome. All studies used VAS for subjective loudness (see Appendix E, Table E2, for full study details for this outcome).

One study¹¹⁶ evaluated the impact of ACRN on subjective loudness (VAS) measured after 12 weeks of treatment, and all groups except placebo (G5) had statistically significant changes relative to baseline scores (within group) for the on stimulation condition; for the off stimulation condition, only G1 and G3 groups showed significant differences relative to baseline. The estimates of effect size based on the standardized mean difference (see Figure 12) would suggest that G1 treatment protocol was favored relative to G5 placebo. However, the study reports that there were no differences for a matched subgroup from G1 (subgroup n=5), relative to placebo group G5 (n=5).

Two studies involved LLLT versus sham LLLT, with one article³⁵ finding no statistical difference in self-reported loudness (measured on a 10 cm VAS, with 0 indicating no tinnitus and 100 indicating the highest loudness level) in the treatment group after 3 months of patient-administered daily treatment (p=0.69). Similarly, the second LLLT study,¹⁰⁸ using Ga-Al-As diode laser administered by a clinician, no differences between groups were found on a 100 mm VAS after 3 weeks of treatment and at the 1 month of followup (mean difference=4.1 favoring placebo; p=0.53).

In the acupuncture study,¹¹⁸ the authors found no differences between groups on active versus sham acupuncture, measured using an undefined VAS, over 5 weeks of followup (mean difference=5.0 favoring active acupuncture; p>0.05).

Strength of Evidence—Self Reported Loudness

There is insufficient evidence that ACRN (one study, 65 participants), LLLT (two studies, 102 participants), and acupuncture (one study, 54 participants) improves self-reported loudness when compared with inactive treatment for idiopathic tinnitus immediately post treatment or after short term followup (Table 17). All the studies measuring this outcome consistently showed no statistical differences between treatment and inactive control groups; however the studies had small sample sizes (less than 30 per group) and it is not clear if this is a factor in the results and as such the studies are considered imprecise. Both LLLT studies showed that the point estimates favored control, but were not statistically significant between groups; the effect sizes were generally small. The study evaluating ACRN consistently favored treatment but only one dose was statistically significant. Risk of bias was high in all studies. Publication bias is assumed as the sample sizes of the studies were small. There is insufficient evidence that ACRN, LLLT, and acupuncture improve subjective loudness, as the criteria for three or more domains were not met.

Table 17. Strength of evidence by medical interventions in the treatment of tinnitus for the outcome of loudness for studies with inactive comparators

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
ACRN vs. sham	N/A	1 ¹¹⁶	High	Unknown	Direct	Imprecise	-1.15 (-2.18, -0.12) to -0.41 (-1.47, 0.64)	Insufficient
Laser therapy vs. sham	N/A	2 ^{35,108}	High	Consistent	Direct	Imprecise	0.23 (-0.34, 0.80) to 13 (-0.40, 0.66)	Insufficient
Acupuncture vs. placebo	N/A	1 ¹¹⁸	High	Unknown	Direct	Imprecise	-0.27 (-0.81, 0.27)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference; vs. = versus

Sleep Disturbance

None of the studies evaluating medical interventions measured the impact on sleep disturbance.

Anxiety Symptoms

One study at high risk of bias¹⁰⁸ evaluated active versus sham LLLT (Ga-Al-As, diode laser) administered by a clinician (Table 15). The State Trait Anxiety Inventory (STAI) was evaluated at baseline and 1 month following treatment. For laser,¹⁰⁸ mean score on the STAI was lower in the LLLT group yet not statistically significant (p=0.74).

Strength of Evidence—Anxiety Symptoms

There is insufficient evidence that LLLT (one study, 50 participants) improves anxiety symptoms relative to sham control in idiopathic tinnitus patients in the short term (Table 18). The study was at high risk of bias, had a small sample size, and had a wide confidence interval (imprecise). The SOE for LLLT for the outcome of anxiety symptoms is insufficient, as the criteria for three or more domains is not met.

Table 18. Strength of evidence by medical interventions in the treatment of tinnitus for the outcome of anxiety symptoms for studies with inactive comparators

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Laser therapy vs. sham	N/A	1 ¹⁰⁸	High	Unknown	Direct	Imprecise	0.39 (-0.18, 0.95)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference; vs. = versus

Depression Symptoms

A single study at high risk of bias¹⁰⁸ evaluated depression symptoms following the use of LLLT (Ga-Al-As, diode laser) administered by a clinician (Table 14). The Beck Depression Inventory (BDI) was evaluated at baseline and 1 month following treatment. After one month of

followup, the difference on the BDI, while favoring the active LLLT group, was small and non-significant (mean difference=0.2; p=0.58).

Strength of Evidence—Depression Symptoms

The evidence is insufficient for the single study that evaluated LLLT (one study, 50 participants) improving depression symptoms relative to sham LLLT in the short term. The study was at high risk of bias, small sample size, and a wide confidence interval (imprecise). The SOE for this single study which used LLLT and reported impact on depression symptoms (using the STAI) was rated as insufficient (Table 19) because the criteria for three or more domains were not met.

Table 19. Strength of evidence by medical interventions in the treatment of tinnitus for the outcome of depression symptoms for studies with inactive comparators

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
Laser therapy vs. sham	N/A	1 ¹⁰⁸	High	Unknown	Direct	Imprecise	0.33 (-0.24, 0.89)	Insufficient

Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference; vs. = versus

Global Quality of Life

None of the studies evaluating medical interventions measured the impact on global QoL (Table 14).

Adverse Effects—Medical Interventions

Adverse effects (AE) addressing unintended effects other than worsening tinnitus symptoms (which are considered in the outcomes of severity, loudness, and discomfort), were considered in this report. In general, AE were not consistently reported, and not specified in the methods of the studies. Table 20 shows the percentage of subjects who dropped out because of AE, whether the study methods specifies the mode of collection of AE, and any treatment emergent events that were reported.

None of the studies in the medical interventions group reported drop-outs related to AE. A single study¹¹⁰ reported a priori methods used to collect AE and employed both passive and active approaches to capture potential events and reported events per treatment group. In general, it would appear that AE were transient and mild in nature; however, it is difficult to report any trends related to specific medical interventions, given that all but one study did not report the methods used to capture AE.

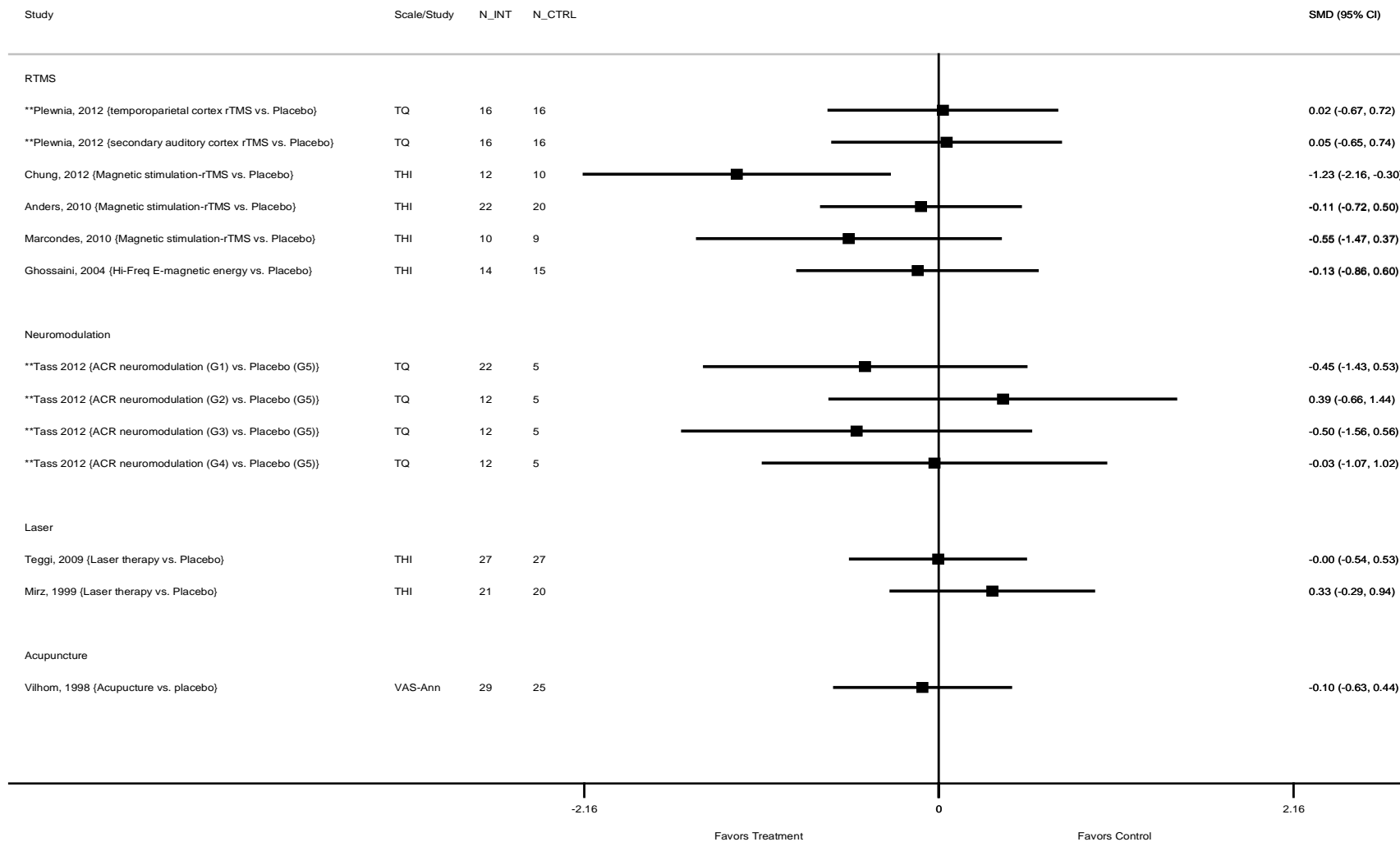
Table 20. Description of reported adverse effects in the medical intervention studies

Medical Intervention Category	Specific Intervention	Dropouts Due to AE	AE Info Collected	Treatment Emergent AE (did not drop out of study) Reason(s)
rTMS and electromagnetic Stimulation	rTMS vs. sham ⁸³	0	NR	Worsening of Tinnitus symptoms (n=2)
	rTMS vs. sham ¹⁰⁵	0	NR	All patients tolerated rTMS without relevant side effects
	rTMS vs. sham ⁸⁸	0	NR	Transient jaw soreness (n=5) Temporary orbital twitching (n=3) Facial myalgia (n=1)
	rTMS vs. sham ¹¹⁰	0	Yes*	Headache (SAC 2, TAC 2, PLC 3), worsening tinnitus (SAC 1, TAC 2, PLC 3), increased sensitivity to noise (TAC 1, PLC 1), painful local sensation (SAC 1), sleep disturbance (SAC 1)
	rTMS vs. rTMS ¹⁰³	0	NR	Treatment was well tolerated. No serious A/E were observed.
	High-Frequency Pulsed Electromagnetic Energy vs. sham ⁹⁴	0	NR	Worsening of Tinnitus symptoms Tx n=4 (26.6%); PI n=5 (35.7%)
ACRN	ACRN vs. sham ¹¹⁶	0	NR	15 AEs occurred in total: 13 AEs during blinded phase, 2 AEs in LTE. Two SAEs (an abdominal pregnancy and avascular necrosis of the femoral head, not associated with treatment) were reported. All other AEs were of mild to moderate intensity and none was permanent. 8 AEs were judged to be treatment related of which 3 AEs were associated with a transient increase of tinnitus loudness; all 3 patients continued treatment into the LTE.
LLLT	LLLT vs. sham ¹⁰⁸	0	NR	Some experienced warmth inside the ear canal No serious untoward AE noticed
	LLLT vs. sham ³⁵	2/4 (50%)	NR	Increase in tinnitus loudness n=2
	Laser + counseling vs. sham + counseling ⁸⁹	0	NR	NR
Acupuncture	Acupuncture vs. sham ¹¹⁸	0	NR	NR

Abbreviations: ACRN = acoustic coordinate reset neuromodulation; AE = adverse effect(s); CBT = cognitive behavioral training; CI = confidence interval; LLLT = low level laser treatment; LTE = longterm evaluation; med/surg = medical/surgical; n = sample size; NR = not reported; NS = not significant; PI = placebo; PLC = placebo; psych/beh = psychological/behavioral; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SAC = secondary auditory cortex; SARI = serotonin antagonist reuptake inhibitor; SMD = standard mean difference; SOE = strength of evidence; SSRI = selective serotonin reuptake inhibitor; TAC = temporoparietal association cortex; Tx = treatment; vs. = versus; WLC = wait list control

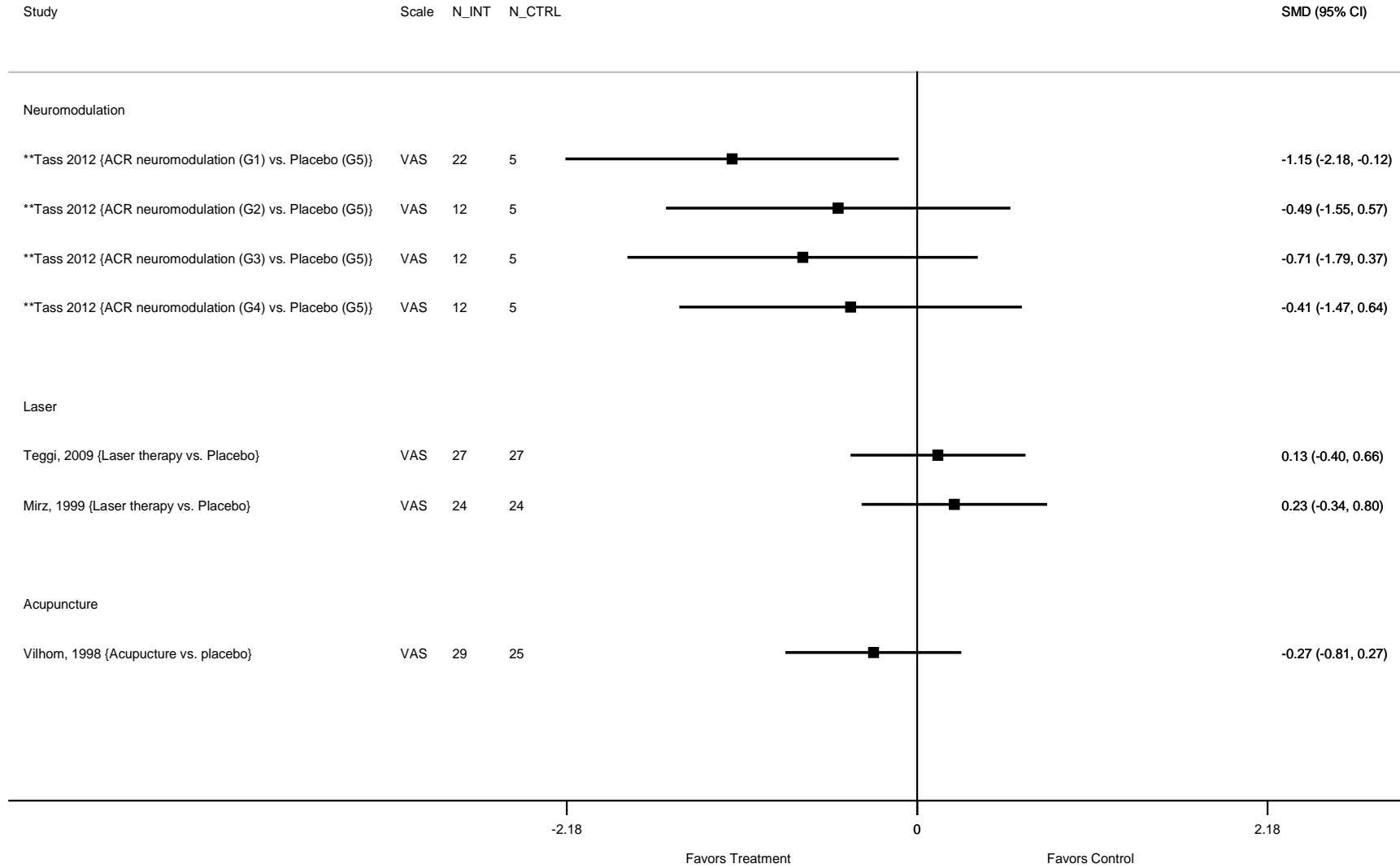
* All patients underwent a standard otolaryngological physical examination as a safety assessment. At every treatment visit, tolerability and safety was assessed by spontaneous adverse effect reports. At baseline and after 2 and 4 weeks of treatment audiologic testing was performed, including subjective tinnitus matching, puretone audiometry, and speech audiometry in quiet using the Freiburg speech test and in noise with the Oldenburg sentence test.

Figure 11. Studies with inactive comparators that evaluate medical interventions and report tinnitus-specific quality of life outcomes



Note: A decrease in score indicates improvement.
******Represent studies with multiple intervention groups.

Figure 12. Studies with inactive comparators that evaluate medical interventions and report subjective loudness outcomes



Note: A decrease in score indicates improvement.
******Represent studies with multiple intervention groups.

Sound Technology Interventions

Key Messages

Four head-to-head studies (with sample sizes per group less than 50) evaluated five different interventions alone and/or in combination with other forms of treatment.^{53,61,92,98}

The interventions compared were:

- TRT with either hearing aids or sound generators,
- information only, with relaxation training, with long-term low-level white noise masking (LTWN), with both relaxation and LTWN
- CBT only, tinnitus education (TE) only, NG with CBT, NG with TE
- Neuromonics with one stage or two stages of stimulus conditions.

All studies had insufficient SOE. No study demonstrated a significant difference between the technologies used in the treatments evaluated on any measure.

Tinnitus-Specific Quality of Life

All studies measured this outcome, but using a variety of measures.

There were no significant differences between treatments in any of the studies, although benefits were reported for both TRT treatments and for both Neuromonics treatments. However, the SOE was insufficient for studies evaluating the effects on sound technology interventions on TSQoL.

Subjective Loudness

All but one study⁵³ evaluated this outcome.

There were no significant differences between treatments in the three studies in which this outcome was measured, although benefits were reported for both TRT treatments. However, the SOE was insufficient for studies evaluating the effects on sound technology interventions on subjective loudness.

Sleep Disturbance

No study in this category evaluated this outcome.

Anxiety

One study⁹⁸ evaluated this outcome.

All groups in the study demonstrated improvement, but adding NG to TE or CBT did not increase benefit and may even have decreased it. However, the SOE was insufficient for studies evaluating the effects on sound technology interventions on anxiety.

Depression

One study⁹⁸ evaluated this outcome, but only for the groups receiving CBT and not for the groups receiving TE because few participants had clinically significant results pre-treatment.

There was no benefit from CBT with or without NG. However, the SOE was insufficient for studies evaluating the effects on sound technology interventions on depression.

Global Quality of Life

Three studies^{61,92,98} evaluated this outcome using a variety of different measures.

Benefit was reported for all interventions involving TRT, but there were no differences depending on the technology used.⁶¹ No benefits were reported in the other two studies. However, the SOE was insufficient for studies evaluating the effects on sound technology interventions on global QoL.

Characteristics of Included Studies

Five publications (four head-to-head studies) were included for KQ2 and were classified into the sound treatment/technology intervention category (Table 21).^{53,61,91,92,98} Two articles reported on the same results^{91,92} and only one⁹² will be discussed in this section. As well, two different interventions were presented in one article and they will be described separately in the intervention section (described as STUDY A and STUDY B).⁹⁸ See Appendix E for the Characteristics of Included Studies Evidence Tables.

Population—Duration and Severity of Tinnitus

The subjects in all of studies were from the general population of those experiencing subjective idiopathic tinnitus. For one study, the duration of time participants had been bothered by their tinnitus before being eligible for the intervention study was a minimum of 6 months.⁹⁸ In other papers, the majority of the participants were identified as having tinnitus for 11 years,⁵³ and 69.5 months.⁶¹ One study did not report on the duration of tinnitus prior to the intervention.⁹²

The severity of the tinnitus was not consistently identified prior to treatment among subjects in the four studies. One article included patients with moderate to severe tinnitus⁵³ while one included individuals with chronic tinnitus.⁹⁸ Two articles did not report on the severity of tinnitus.^{61,92} The presumed etiologies of tinnitus were described as hearing loss,⁹⁸ and bilateral hearing loss.⁶¹ Presumed etiology was not reported in two studies.^{53,92} Audiological factors at study enrollment included decreased sound tolerance,⁵³ and borderline between category 1 and category 2 according to the Jastreboff classification with hearing loss (HL) ≤ 25 dB HL at 2 kilohertz (kHz) and HL ≥ 25 dB HL at frequencies higher than 2 kHz.⁶¹ Two articles did not report on audiological factors at enrollment.^{92,98}

Head-to-Head Interventions

All four studies^{53,61,92,98} categorized under the sound treatments/technology category (Table 21, and Appendix E, Table E3.) focused on head-to-head comparison including: hearing aids versus sound generators;⁶¹ one stage intermittent perception plus two stage complete covering of perception initially, then intermittent;⁵³ information only, information plus relaxation training, information plus long-term low level white noise (LTWN), information plus relaxation training plus LTWN;⁹² and cognitive behavioral therapy (CBT) with noise generator (NG), CBT alone, tinnitus education (TE) plus NG, and TE with no NG.⁹⁸

Table 21. Interventions and comparators used in studies that evaluate sound treatment/technology interventions and outcomes

Sound Treat Intervention	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects
	HEAD-TO-HEAD							
1	Hearing aids vs. SG Parazzini, ⁶¹ 2011				subjective	VAS	THI	NR
2	Neuromonics Tinnitus Treatment – 2 nd study One-stage: Intermittent perception Two-stage: complete covering of perception initially, then intermittent Davis, ⁵³ 2007				VAS		TRQ VAS	NR
3	Group I: Information Only Group IR: information plus relaxation training Group ID: information plus LTWN Group IDR: information plus relaxation plus LTWN Dineen, ^{91,92} 1997,1999				VAS	DSP (total stress)	TRQ, VAS VAS (coping), change in awareness	NR
4	CBT with NG CBT alone Hiller, ⁹⁸ 2004 STUDY A		WI		VAS		TQ, T-cog	NR
	TE plus NG TE no NG Hiller, ⁹⁸ 2004 STUDY B		WI		VAS	SCL-90R, PSDI	TQ, T-cog, VAS, Diary of symptoms	NR

Abbreviations: DSP=Derogatis Stress Profile; LTWN = long-term low level white noise; med/surg = medical/surgical; NG = noise generator; NR = not reported; PDPSDI = Positive Symptom Distress Index; QoL = Quality of Life; SG = sound generator; T-cog = Tinnitus Cognition Scale; TE = tinnitus education; THI = Tinnitus Handicap Inventory; TQ = Tinnitus Questionnaire; VAS = visual analogue scale; WI = Whiteley Index

Outcomes

Most studies reported data on more than one outcome (Table 21, also Appendix E, Table E3.). The outcome measurement instruments used varied for the same outcomes (Table 22). For example, four different instruments were used to measure the outcome of TSQoL. Upon discussion with clinical experts, the following decisions regarding outcomes were made. All results that addressed the outcomes of interest were extracted. However, when a clinical outcome was measured using multiple scales within the same study, the outcome was reported once for that study. Data was extracted for the most widely used scale for that outcome, even if both scales were validated. This approach was implemented to facilitate better comparability between studies. The results of any studies that used the terms ‘annoyance’ or ‘distress’ were included to describe outcomes in the category of ‘discomfort.’

Table 22. Outcome measurements used in sound technology intervention studies

Outcome	Outcome Measurement Used
Anxiety Symptoms	WI (Whiteley Index) ⁹⁸
Subjective loudness	VAS (Visual Analogue Scale) ^{53,92,98} Subjective ⁶¹
Global Quality of Life	VAS (Visual Analogue Scale) ⁶¹ DSP(The Derogates Stress Profile) ⁹² SCL-90R (Symptom Checklist, general psychopathology) ⁹⁸
Tinnitus-Specific Quality of Life	TRQ (The Tinnitus Reaction Questionnaire) ^{53,92} TQ (Tinnitus Questionnaire) ⁹⁸ VAS (Visual Analogue Scale) ^{53,92,98} TRSS (Tinnitus-Related Self-Statements Scale) ¹⁸

Setting

The research settings were a tinnitus clinic,⁶¹ a university hearing clinic,⁹² and an outpatient department.⁹⁸ One paper did not report the setting (Appendix E, Table E3).⁵³

Country

The studies were carried out in Australia^{53,92} the United States and Italy,⁶¹ and Germany.⁹⁸

Sources of Funding

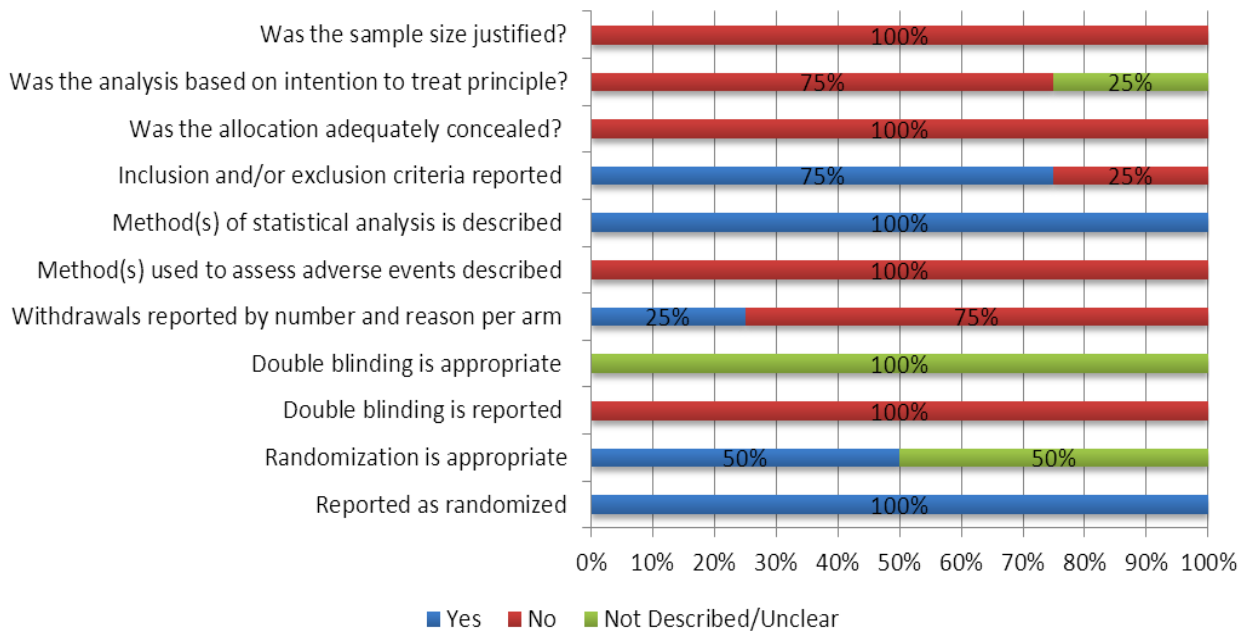
Sources of funding included the Australian Commonwealth Government via a Biotechnology Innovation Fund,⁵³ grants from a Tinnitus Research Initiative,⁶¹ and financial support from the German Tinnitus Association.⁹⁸ One paper did not reveal the source of funding.⁹²

Risk of Bias for Sound Technologies

The risk of bias in the four studies was mixed (n=3 fair; n=1 poor).^{53,61,92,98} All authors reported their studies as randomized, with appropriate randomization in 50 percent (n=2) of articles^{53,61} and not described in two.^{92,98} All articles did not involve double-blinding due to the nature of the interventions. Three (75 percent) articles reported the inclusion/exclusion criteria,^{53,61,98} and all described the statistical methods used (Figure 13).

Issues with risk of bias in the RCTs included a lack of reporting on withdrawals (n=3, 75 percent),^{53,61,92} no description of methods to assess adverse effects (n=4, 100%),^{53,61,92,98} inadequate concealment of allocation (n=4, 100%),^{53,61,92,98} analysis not based on intention-to-treat principle (n=3, 75%),^{61,92,98} and inadequate justification of sample size (n=4, 100%).^{53,61,92,98}

Figure 13. Distribution of methodological risk of bias criteria of randomized controlled trials for the sound technology interventions



Results for Sound Technologies by Outcome

Tinnitus-Specific Quality of Life

All studies measured the effectiveness of treatment using a tinnitus-specific measure; however, a variety of different measures were used in each study, including the TRQ and a single-item VAS,^{53,92} the TQ and VAS,⁹⁸ and the THI.⁶¹ A significant reduction in tinnitus severity on the THI was found for the TRT treatment delivered with either sound generators or open ear hearing aids, but no difference between treatments was found.⁶¹ A significant reduction in tinnitus disturbance on the TRQ was reported for a one-stage version and a two-stage version of Neuromonics tinnitus treatment; however, there was no significant difference in the reduction found for the two versions of the treatment which differed in terms of when and to what extent tinnitus perception was totally covered up or intermittent.⁵³ Note that the author of this study developed Neuromonics and continues to work for the company. In a study comparing four treatments offering information, white noise, relaxation or combinations of these components, no differences between treatments was found on the TRQ.⁹² No significant effect of intervention was found on the TQ or the Tinnitus Cognition Scale (T-Cog) in a study⁹⁸ investigating whether use of a low level white-noise generator (NG) would enhance the effects of CBT, or tinnitus education (TE), with the degree of tinnitus-related stress determined using the Structured Tinnitus Interview (STI).

Overall, significant benefits of treatment in terms of TSQoL measures were reported in half of the studies, but there were no significant differences between the treatments that were compared using such measures.

Subjective Loudness

All but one of the studies^{61,92,98} evaluated the effects of intervention on the subjective loudness of the tinnitus.^{61,92,98} Significant reductions in subjective loudness were reported in one study⁶¹ in which TRT was delivered with either sound generators or open ear hearing aids; however, there was no difference between treatments on this outcome measure. In a study comparing four treatments with information, white noise, relaxation or combinations of these components, no change in subjective loudness was found for any of the treatments.⁹² No significant differences between treatments in reduction of subjective loudness were reported in a study comparing the benefit of combining the use of NG with either CBT or TE.⁹⁸

Overall, it seems that the effects of intervention on subjective loudness did not differentiate the interventions that were compared.

Sleep Disturbance

No studies evaluated the effects of the interventions on sleep.

Anxiety

Only one study⁹⁸ evaluated the effects of intervention on anxiety. In one study⁹⁸ that sought to determine if the addition of sound stimulation provided by the use of low level white-noise generators would enhance the effects of CBT or TE, the Whiteley Index (WI) was used to measure health-related anxieties. All groups demonstrated improvement on the WI, but no statistically significant additional benefit due to NG was observed when it was combined with either TE or CBT and in fact, adding NG seemed to have a deleterious effect on the WI outcome measure.⁹⁸

Depression

Only one study reported the effects of the interventions on depression symptoms. No significant effect of CBT treatment either with or without NG was found when the SCL-90R was used to measure depression,⁹⁸ but changes due to the TE with or without NG were not reported because not all participants had clinically significant conditions pre-treatment.

Global Quality of Life

Global quality of life was measured in three studies,^{61,92,98} using a number of different measurement tools. A significant reduction in tinnitus severity on the single item “effect on life” VAS was found for the TRT treatment delivered with either sound generators or open ear hearing aids, but no difference between treatments was found.⁶¹ In a study comparing four treatments with information, white noise, relaxation or combinations of these components, no differences between treatments were found on the DSP measure of life stress.⁹² The SCL-90R of the Positive Symptom Distress Index (PSDI) and the Dysfunctional Analysis Questionnaire (DAQ) were used to measure psychopathology and psychosocial functioning, respectively,⁹⁸ with no significant effects of treatment being found for the CBT intervention with or without NG, while changes due to treatment were not reported for the TE intervention with or without NG because not all participants had clinically significant conditions pre-treatment.

Overall, although benefits of treatment were reported for TRT, no benefits were reported for the other interventions and no differences between treatments were discernible using this outcome.

Strength of Evidence—Sound Technologies

The types of sound technologies and comparator groups within each study were markedly diverse. For this reason we did not prepare formal SOE tables as all would have a similar rating of insufficient irrespective of the outcome being measured. All the studies evaluating sound technologies relative to different active comparators were considered to be at high risk of bias and unknown consistency. The very small sample sizes within the studies is a factor contributing to the rating of ‘imprecise’. Overall, there is insufficient information to judge the SOE for the head-to-head studies evaluating sound technologies.

Psychological and Behavioral Interventions

Key Messages

Nineteen studies were included as psychological and behavioral interventions for KQ2. They were organized into four general sub-categories: CBT, TRT, relaxation, and other.

- Ten compared some form of CBT to an inactive control and six compared CBT to another treatment.
- Two compared TRT to an inactive control and three compared TRT to another treatment,
- Three compared some form of relaxation therapy to an inactive control and one compared relaxation to another treatment.
- Six studies evaluated some other type of psychological/behavioral therapy compared to an inactive control and one involved head-to-head comparisons between treatments.

The research settings were varied; some studies recruited patients from ENT, audiology or psychology clinics at hospitals or universities and others recruited volunteers using newspapers or the internet.

Most studies recruited participants from the general population of middle-aged or older adults experiencing subjective idiopathic tinnitus. Three studies focused on specific subpopulations: veterans,⁹⁷ industrial workers,⁸¹ and older adults.⁸⁴

Eligibility criteria in terms of duration and severity of tinnitus varied.

Some studies restricted participation to those without significant depression or anxiety.

Nine studies in the psychological/behavioral grouping have sample sizes greater than 20 subjects per group and most had less than 50 subjects per group.

Subjective Loudness

Eight RCT studies with WLCs investigated the effects of 16 interventions on subjective loudness. Although benefits in subjective loudness were suggested by two CBT interventions, CBT combined with biofeedback¹⁸ and a self-help book with telephone therapy,¹⁰⁰ overall, there was low SOE for no effect in subjective loudness from CBT.

SOE was insufficient for other interventions.

Sleep Disturbance

Five RCT studies with WLCs investigated the effects of nine interventions on sleep. Although benefits in sleep were suggested by two studies in the CBT sub-category, biofeedback-based CBT,¹⁸ and self-help book with telephone therapy,¹⁰⁰ overall, there was low SOE for no effect in sleep from CBT.

SOE was insufficient for other interventions.

Anxiety Symptoms

Five RCT studies with WLCs investigated anxiety symptoms in nine interventions as one of the main outcomes^{57,62,84} or as a secondary outcome^{100,120} that was compared to a WLC group. Although benefits in anxiety were noted in one study in the CBT sub-category: self-help book with telephone therapy,¹⁰⁰ overall, there was low SOE for no effect in anxiety from CBT.

SOE was insufficient for other interventions.

Depression Symptoms

Eleven RCT studies with WLCs investigated the effects of 22 interventions on depression symptoms, but depression was a primary outcome in only two studies^{57,62} and a secondary outcome in the others. Although benefits in depression were suggested for four interventions in the CBT sub-category: self-help with telephone therapy,¹⁰⁰ CR with or without ACI,⁹⁶ and biofeedback-based CBT¹⁸ and benefit was also suggested for two interventions using relaxation and distraction,^{10,62} overall, there was low SOE for no effect in depression symptoms from CBT.

SOE was insufficient for other interventions.

Global Quality of Life

Six RCT studies with WLCs investigated the effects of 11 interventions on global quality of life. Although benefits in global quality of life were suggested for biofeedback-based CBT¹⁸ and bibliotherapy,¹⁰⁴ and marginally for psycho-physiologic therapy,¹¹² overall, there was low SOE for no effect in global QoL from CBT and bibliotherapy.¹⁰⁴

SOE was insufficient for other interventions.

Characteristics of Included Studies

A total of 19 RCT articles^{10,17,18,57,62,64,81,84,87,95-97,100-102,104,112,120,121} evaluated interventions in the psychological and behavioral domain (Table 23, Appendix E, Table E4). The interventions in this domain are organized in four sub-categories, including those involving primarily some form of cognitive behavioral therapy (CBT), a version of tinnitus retraining therapy (TRT), relaxation, or other therapies (e.g., education, Qigong, yoga).

Population—Duration and Severity of Tinnitus

The subjects in the majority of studies were from the general population of those experiencing subjective idiopathic tinnitus. Three studies focused on specific subpopulations of veterans,⁹⁷ individuals from various industrial organizations,⁸¹ and older adults.⁸⁴

For some studies, the duration of time participants had been bothered by their tinnitus before being eligible for the intervention study was a minimum of 3 months.⁸⁷ In other studies tinnitus had to have been bothersome for greater than 3 months,^{81,101,121} and at least 6 months.^{18,57,95,96,100,112} In other papers, the majority of the participants were identified as having tinnitus for 3 years or more,⁹⁷ 8.3 years,¹²⁰ 9.4 years,¹⁰ and 13 years.⁸⁴ Other publications did not report on the duration of tinnitus prior to the intervention.^{10,17,62,64,104}

The severity of the tinnitus was not consistently identified prior to treatment among subjects in the 19 publications. Some studies included an assessment by an otolaryngologist (ENT), audiologist or a physician being consulted about tinnitus;^{57,95,96,100} one study included only persons who had not received treatment elsewhere, or persons for whom previous treatments had failed.⁶² In the inclusion criteria, tinnitus was identified as having to be a ‘main’ or ‘major’ complaint,⁸⁷ perceived as constant,¹⁰ ‘sufficiently bothersome to warrant intervention’,⁹⁷ and as

‘disabling chronic uni- or bi-lateral.’¹⁰⁸ Some studies required specific scores on tinnitus severity scales to meet study inclusion criteria. These include: a score of 10 or greater on the Tinnitus Reaction Questionnaire (TRQ);^{100,101} a distress score greater than 17 points on the TRQ;^{95,96} a score greater than 46 (high annoyance) on the Tinnitus Questionnaire (TQ) Modified version;¹⁸ a score of greater than 40 on nine scales assessing the disruptive effects of tinnitus;¹⁷ a Visual Analogue Scale (VAS) score (range=0 to 10) of greater than 3;¹¹² ≥ 30 on the Tinnitus Handicap Inventory (THI) scale;¹²⁰ and a tinnitus of grade 2 or 3.^{10,147}

Interventions

There is considerable heterogeneity among the treatments categorized as Psychological and Behavioral Interventions and also within each of the four sub-categories of CBT, TRT, relaxation and other. For the purposes of the present review, general characteristics of the therapies rather than the specific details of the therapeutic protocols guided the placement of studies in the sub-categories (Table 23).

CBT does not exist as a distinct therapeutic technique and has no strict definition. It is a form of psychotherapy that emphasizes the important role of thinking in how we feel and what we do. Insofar as it involves psychotherapy, it features an interaction between a clinician and patient, but the format could be individual or group, and it could be delivered in person or at a distance with telephone or internet contact. Studies were considered to be in the CBT subcategory if the author described the intervention as CBT or as being CBT-based or involving tinnitus coping training (TCT) or a cognitive approach such as attention control and imagery (ACI), cognitive restructuring (CR), or acceptance and commitment therapy (ACT). CBT for the elderly⁸⁴ was compared to no treatment, and internet CBT⁵⁷ and TCT¹⁷ were compared to an inactive control. CBT combined with biofeedback¹⁸ and a psychophysiological-oriented intervention combining CBT and relaxation components¹¹² were compared to WLCs. In one study,¹⁰² comparisons were made between four conditions: a WLC, the same CBT intervention administered by two different clinicians (TCT1 and TCT2), and yoga. In another study,⁹⁶ comparisons were made between three conditions: a WLC and two types of cognitive intervention, ACI and CR provided alone or in combination. In another study,⁹⁵ comparisons were made between three conditions: a WLC, CBT with education and education alone. An additional two studies compared CBT to other treatments: an information only intervention⁸¹ or to internet-based self-help.¹⁰¹ A final study¹²¹ compared TCT to two other interventions, habituation-based treatment (HT) and education.

TRT is a well-known intervention that features both the use of sound and a particular type of structured directive counseling. Studies were placed in the TRT category if the intervention was described as TRT or included a component based on TRT principles, and it was compared to either an inactive control or in a head-to-head comparison to another psychological/behavioral intervention. Three articles^{64,97,120} evaluated forms of TRT with an emphasis on the behavioral aspect of TRT (note that one other article⁶¹ focused on comparing the sound technology aspect of TRT and it was included in the section on Sound Technology Interventions). In one study, interventions in which TRT principles were applied to either a traditional support group or to group education and counseling were compared to a WLC or each other.⁹⁷ In the other study,¹²⁰ TRT was compared to a WLC and to ACT. A final additional study compared a combination of CBT and TRT to usual care.⁶⁴

Relaxation may be incorporated into the protocols of many interventions, but studies evaluating interventions in which relaxation was the main approach were allocated to the relaxation sub-category. Three articles^{10,17,62} compared interventions focused on relaxation to

WLCs. In one of the studies,⁶² the relaxation therapy was administered in the same way to four groups, with instructions that were either neutral or counter-demand (participants were told not to expect improvements until after five weeks) and with two groups recruited for each instruction condition; thus, comparisons between the four groups and the WLC could be made as well as comparisons between groups receiving the same or different instructions.

The “other” sub-category was used to group studies evaluating psychological/behavioral interventions not assigned to the CBT, TRT or relaxation sub-categories. Some of the studies involving CBT, TRT and relaxation interventions listed above also included comparisons between other treatments and a WLC, including: education,¹⁷ bibliotherapy,¹⁰⁴ Qigong therapy,⁸⁷ and yoga.¹⁰² Finally, one study¹²¹ included a head-to-head comparison between HT and education.

Comparators

Ten articles^{17,18,57,84,95,96,100,102,112,120} had an inactive control, with either no treatment⁸⁴ or a WLC (WLC)^{17,18,57,95,96,100,102,112,120} compared to various forms CBT administered either alone or in combination with other treatments. These, along with the head-to-head comparisons are detailed in Table 23.

Comparators for the articles assessing TRT included no treatment⁹⁷ and WLC.¹²⁰ The comparators for relaxation therapy^{10,17,62} and for other interventions were also all WLC.^{17,87,102,104}

Table 23. Interventions and comparators used in studies that evaluate psychological and behavioral interventions and outcomes

Psych/Beh Intervention	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects	
CBT/CBT Combination	INACTIVE COMPARISONS								
	1	CBT vs. no treatment Andersson, ⁸⁴ 2005		HADS-A ⁺ , ASI	HADS-D			TRQ	NR
	2	CBT via the internet vs. WLC Andersson, ⁵⁷ 2002	VAS	HADS-A ⁺ , ASI	HADS-D	VAS		TRQ ⁺ , VAS-Ann, VAS-Ctrl	NR
	3	CR vs. WLC Henry JL and Wilson PH, ⁹⁶ 1998			BDI			TRQ ⁺ , TEQ, THQ (handicap), TCSQ (coping) TCQ	NR
		CR combined with ACI vs. WLC Henry JL and Wilson PH, ⁹⁶ 1998			BDI			TRQ ⁺ , TEQ, THQ (handicap), TCSQ (coping) TCQ	NR
		ACI vs. WLC, Henry JL and Wilson PH, ⁹⁶ 1998			BDI			TRQ ⁺ , TEQ, THQ (handicap), TCSQ (coping) TCQ	NR
	4	CBT & Education vs. WLC Henry JL and Wilson PH, ⁹⁵ 1996			BDI	Self-report		TRQ ⁺ , TEQ, THQ (handicap), TCSQ (coping), TCQ (Awareness)	NR
	5	CBT- biofeedback-based vs. WLC Weise, ¹⁸ 2008	VAS ⁺ , TQ-sub		BDI	VAS	GSI SCL-90R	TQ ⁺ , VAS TRSS (catastrophizing), TRCS (helplessness)	NR
	6	TCT1 vs. WLC Kroner-Herwig, ¹⁰² 1995	Diary, TQ subs		Dep-Skala	Diary	Bef-Skala Bes-Liste	TQ Diary	NR
		TCT2 vs. WLC Kroner-Herwig, ¹⁰² 1995	Diary, TQ subs		Dep-Skala	Diary	Bef-Skala Bes-Liste	TQ Diary	NR
7	TCT vs. WLC Kroner-Herwig, ¹⁷ 2003			ADS	Diary	SCL-90R GSI	TDI TQ TC (COPE subscales)	NR	
8	Psychophysiological therapy vs. WLC, Rief, ¹¹² 2005				Diary	HRLS ⁺ GSI SCL-90R	TQ ⁺ , emotional cognitive distress	None	

Table 23. Interventions and comparators used in studies that evaluate psychological and behavioral interventions and outcomes (continued)

Psych/Beh Intervention	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects	
CBT/CBT Combination (continued)	INACTIVE COMPARISONS (contued)								
	9	Self-help book and brief phone therapy vs. WLC Kaldo, ¹⁰⁰ 2007	ISI	HADS-A	HADS-D	VAS		THI (handicap) TRQ, VAS	NR
	10	ACT vs. WLC, Westin, ¹²⁰ 2011	ISI	HADS-A	HADS-D		QoLI	THI (Tinnitus Impact)	None
	HEAD-TO-HEAD COMPARISONS								
	1	CBT vs. Information only Abbott, ⁸¹ 2009	VAS	DASS-A	DASS-D	VAS	WHO-QoL	X TRQ, VAS, OSI-R (occupational)	None
	2	Intervention: Internet based self help Control (usual care) vs. Standard group CBT Kaldo, ¹⁰¹ 2008	ISI	HADS-A	HADS-D	VAS		THI TRQ, VAS	NR
	3	CBT vs. ACI Henry JL and Wilson PH, ⁹⁶ 1998			BDI			TRQ, TEQ, THQ (handicap), TCSQ (coping) TCQ	NR
		CBT vs. CBT combined with ACI Henry JL and Wilson PH, ⁹⁶ 1998			BDI			TRQ, TEQ, THQ (handicap), TCSQ (coping) TCQ	NR
		ACI vs. CBT combined with ACI Henry JL and Wilson PH, ⁹⁶ 1998			BDI			TRQ, TEQ, THQ (handicap), TCSQ (coping) TCQ	NR
	4	CBT & Education vs. Education WLC Henry JL and Wilson PH, ⁹⁵ 1996			BDI	Self-report		TRQ, TEQ, TCSQ(coping), TCQ	NR
	5	TCT1 vs. TCT2 Kroner-Herwig, ¹⁰² 1995	Diary TQ		Dep-Skala	Diary	Bef-Skala Bes-Liste	TQ Diary	NR
		TCT2 vs. yoga Kroner-Herwig, ¹⁰² 1995	Diary TQ		Dep-Skala	Diary	Bef-Skala Bes-Liste	TQ Diary	NR
	7	TCT vs. EDU Zachriat, ¹²¹ 2004				Diary	VEV	TQ, TCQ, JQ, Diary (awareness)	NR
	TCT vs. HT Zachriat, ¹²¹ 2004				Diary	VEV	TQ, TCQ, JQ, Diary (awareness)	NR	

Table 23. Interventions and comparators used in studies that evaluate psychological and behavioral interventions and outcomes (continued)

Psych/Beh Intervention	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects
TRT	INACTIVE CONTROL							
	1 Group education counseling (TRT principles) vs. no treatment Henry, ⁹⁷ 2007						TSI	None
	2 TRT vs. WLC, Westin, ¹²⁰ 2011	ISI	HADS-A	HADS-D		QoLI	THI (Tinnitus Impact)	None
	HEAD-TO-HEAD							
	1 CBT with TRT vs. usual care or no treatment Cima, ⁶⁴ 2012			HADS		HUI	TQ THI (impairment)	None
	2 TRT vs. ACT, Westin, ¹²⁰ 2011	ISI	HADS-A	HADS-D		QoLI	THI (Tinnitus Impact)	None
3 Group education counseling (TRT principles) vs. Traditional support group Henry, ⁹⁷ 2007							TSI	None
Relaxation	INACTIVE COMPARATOR							
	1 Relaxation therapy vs. WLC Scott, ¹⁰ 1985			Self-report-R	Self-report-D		Self-report-D	Yes
	2 Relaxation therapy Counter-demand vs. WLC Ireland, ⁶² 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
	Relaxation therapy Neutral-demand. vs. WLC Ireland, ⁶² 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
	Relaxation therapy Counter-demand -2vs. WLC Ireland, ⁶² 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
	Relaxation therapy Neutral-demand -2vs. WLC Ireland, ⁶² 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
	3 Relaxation vs. WLC Kroner-Herwig, ¹⁷ 2003				ADS	Diary	GSI SCL-90R	TDI (disability), TQ TC (COPE-subcales)

Table 23. Interventions and comparators used in studies that evaluate psychological and behavioral interventions and outcomes (continued)

Psych/Beh Intervention	Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QoL	Tinnitus-Specific QoL	Adverse Effects	
Relaxation (cont'd)	HEAD-TO-HEAD								
	1	Relaxation therapy Counter-demand vs. Neutral Demand Ireland, ⁶² 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
	2	Relaxation therapy-2 vs. Neutral-demand-2 Ireland, ⁶² 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
Other	INACTIVE COMPARATOR								
	1	Education vs. WLC Kroner-Herwig, ¹⁷ 2003			ADS	Diary	GSI SCL-90R	TDI (disability), TQ* TC (COPE-subcales)	NR
	2	Education alone vs. WLC Henry JL and Wilson PH, ⁹⁵ 1996			BDI	Self-report		TRQ, TEQ THQ (handicap), TCSQ (coping), TCQ (Awareness)	NR
	3	Traditional support group vs. no treatment Henry, ⁹⁷ 2007						TSI	None
	4	Bibliotherapy vs. WLC Malouff, ¹⁰⁴ 2010					GHQ-12	TRQ	None
	5	Qigong therapy vs. WLC Biesinger, ⁸⁷ 2010						TBF-12*, VAS	None
	6	Yoga vs. WLC Kroner-Herwig, ¹⁰² 1995	Diary TQ		Dep-Skala	Diary	Bef-Skala Bes-Liste	TQ	NR
		HEAD-TO-HEAD							
1	EDU vs. HT Zachriat, ¹²¹ 2004				Diary	VEV	TQ, TCQ, JQ, Diary(awareness)	NR	

Abbreviations: ACI = attention control and imagery training; ACT = acceptance and commitment therapy; ADS = A Depression Scale, The German version of CES-D “Center for Epidemiologic Studies Depression scale”; Ann = annoyance; ASI = Anxiety Sensitivity Index; BDI = Beck Depression Inventory; CBT = cognitive behavioral training; CR = cognitive restructuring; DASS-A = Depression and Anxiety Stress Scale; DASS-D = Depression and Anxiety Stress Scale; EDU = educational control-group; EDU = education; GHQ = general health questionnaire; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale – Depression subscale; HRLS = health-related life satisfaction; HT = habituation-based treatment; ISI = Insomnia Severity Index; JQ = Jastreboff Questionnaire; NR = not reported; OSI-R = Occupational Stress Inventory–Revised; psych/beh = psychological/behavioral; QoL = Quality of Life; QoLI = Quality of Life Questionnaire Instrument; SCL-90R = Symptom Checklist, general psychopathology; STAI = State-Trait Anxiety Inventory; TBF-12 = Tinnitus Questionnaire; TCT = tinnitus coping therapy; TCQ = Tinnitus Cognitions Questionnaire; TCSQ = Tinnitus Coping Strategies Questionnaire; TDI = Tinnitus Disability Questionnaire; THI = Tinnitus Handicap Inventory; THQ = Tinnitus Handicapped Questionnaire; TQ = Tinnitus Questionnaire; TRCS = The Tinnitus-Related Control Scale; TRQ = The Tinnitus Reaction Questionnaire; TRSS = Tinnitus-Related Self-Statements Scale; TRT = tinnitus retraining therapy; TSI = Tinnitus Severity Index; VAS = visual analogue scale; VEV = changes in wellbeing and adaptive behavior; vs. = versus; WLC = wait list control. *Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Outcomes

Most studies reported data on more than one outcome (Table 23). The outcome measurement instruments used varied for the same outcomes (Table 24). For example, 19 different instruments were used to measure the outcome of TSQoL. Upon discussion with clinical experts, the following decisions regarding outcomes were made. All results that addressed the outcomes of interest were extracted. However, when a clinical outcome was measured using multiple scales within the same study; the outcome was reported once for that study. Data was extracted for the most widely used scale for that outcome, even if both scales were validated. This approach was implemented to facilitate better comparability between studies. The results of any studies that used the terms “annoyance” or “distress” were included to describe outcomes in the category of “discomfort.”

Table 24. Outcome measurements used in psychological and behavioral intervention studies

Outcome	Outcome Measurement Used
Tinnitus-Specific Quality of Life	TRQ (The Tinnitus Reaction Questionnaire) ^{57,81,84,95,96,100,101,104} TEO (Tinnitus Effects Questionnaire) ^{95,96} THQ (Tinnitus Handicapped Questionnaire) ^{95,96} TCSQ (Tinnitus Coping Strategies Questionnaire) ^{95,96} TCQ (Tinnitus Cognitions Questionnaire) ^{95,96,121} TQ (Tinnitus Questionnaire) ^{17,18,64,112,121} VAS (Visual Analogue Scale) ^{18,57,81,87,100,101} TRSS (Tinnitus-Related Self-Statements Scale) ¹⁸ TRCS (The Tinnitus-Related Control Scale) ¹⁸ TCT (Tinnitus Coping Training) ¹⁷ OSI-R (Occupational Stress Inventory–Revised) ⁸¹ THI (Tinnitus Handicap Inventory) ^{64,100,101,120} TSI (Tinnitus Severity Index) ⁹⁷ Self-report Direct and Retrospect ^{10,62} TDI (Tinnitus Disability Questionnaire) ¹⁷ JQ (Jastreboff Questionnaire) ¹²¹ Diary (awareness) ¹²¹ TBF-12 (Tinnitus Questionnaire) ⁸⁷ Diary-D,I,C,TQPQ, TQSC ^{102,121}
Subjective loudness	VAS (Visual Analogue Scale) ^{18,57,81,100,101} Self-rated/reported scale/score ^{10,62,95} Diary ^{17,102,112,121}
Sleep Disturbance	VAS (Visual Analog Scale) ^{18,57,81} ISI (Insomnia Severity Index) ^{100,101,120} TQ (Tinnitus Questionnaire subscale – sleep disturbance) ^{18,102} Diary ¹⁰²
Anxiety Symptoms	HADS-A (Hospital Anxiety and Depression Scale – Anxiety subscale) ^{57,84,100,101,120} DASS-A (Depression and Anxiety Stress Scale) ⁸¹ STAI (State-Trait Anxiety Inventory) ⁶² ASI (Arabic Scale of Insomnia) ^{57,84}
Depression Symptoms	HADS-D (Hospital Anxiety and Depression Scale – Depression subscale) ^{57,84,100,101,120} BDI (Beck Depression Inventory) ^{18,62,95,96} DASS-D (Depression and Anxiety Stress Scale) ⁸¹ ADS (A Depression Scale, The German version of CES-D “Center for Epidemiologic Studies Depression scale”) ¹⁷ Self-report Retrospect ¹⁰ HADS (Hospital Anxiety and Depression Scale - Depression and Anxiety composite) ⁶⁴ Depressivitäts-Skala ¹⁰²

Table 24. Outcome measurements used – Psychological/behavioral interventions (continued)

Outcome	Outcome Measurement Used
Global Quality of Life	HUI-3 (Health Utilities Index-3) ⁶⁴ GSI (Global Severity Index – Symptom Checklist self-rating questionnaire) ¹⁸ WHO-Social (Quality of Life Questionnaire) ⁸¹ QoLI (Quality of Life Questionnaire Instrument) ¹²⁰ SLR-90R (Symptom Checklist self-rating questionnaire) ¹⁷ HRLS (psychological symptoms short form of SCL-90R) ¹¹² GSI (General Symptomatic Index) ¹¹² GPD ¹⁰⁴ VEV (Changes in wellbeing and adaptive behavior induced by treatment which go beyond modification of tinnitus related illness) ¹²¹ Befindlichkeits-Skala, Beschwerden liste ¹⁰² TQ ¹⁰²

Setting

The research settings were in departments of audiology,^{10,102,120} psychology,¹²¹ psychology outpatient,¹⁸ psychotherapy outpatient,¹¹² university clinic,⁶² hospital (department not reported),⁹⁷ clinic,^{62,64,101} phone/mail,¹⁰⁰ newspaper and radio advertisements,⁹⁶ and the internet.^{57,81,84,101,104} Three papers did not report the research setting.^{17,87,95}

Country

The studies were carried out in several different countries: Sweden;^{10,57,84,100,101,120} the United States;⁹⁷ Australia;^{62,81,95,96,104} Germany;^{17,18,87,102,112,121} and the Netherlands.⁶⁴

Sources of Funding

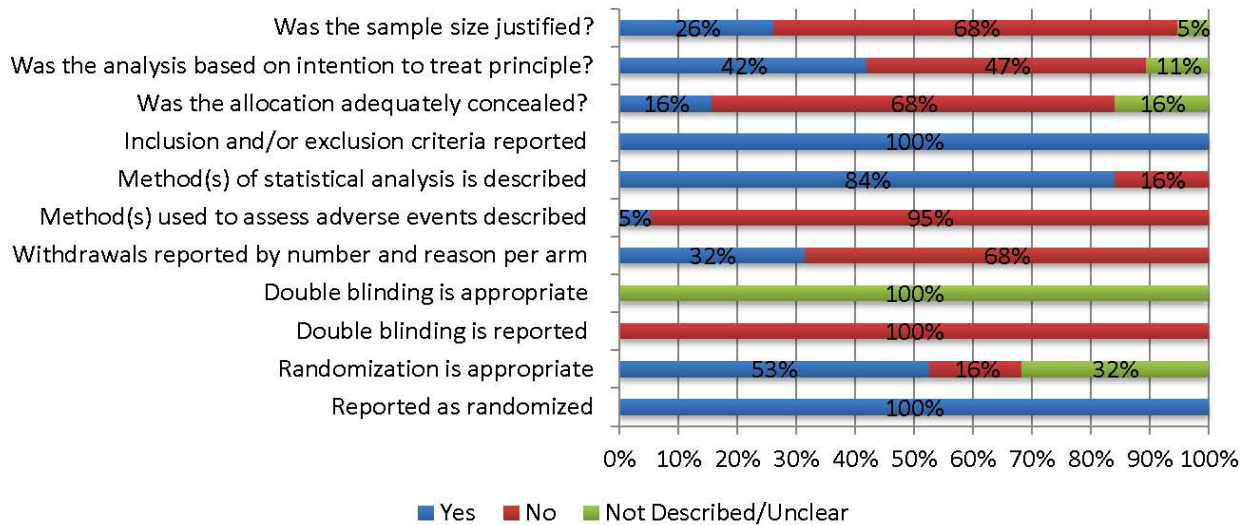
Sources of funding were not reported in seven studies.^{62,87,95,96,101,102,112} Twelve publications received funding from research councils, foundations, and government departments and non-profit associations.^{10,17,18,57,64,81,84,97,100,104,120,121}

Risk of Bias for Psychological/Behavioral Interventions

The risk of bias in the 19 RCTs evaluating psych/behavioral interventions was mixed (n=9 fair;^{18,81,87,96,97,100,112,120,121} n=8 poor;^{10,17,62,84,95,101,102,104} and n=2 good.^{57,64} All authors reported their studies as randomized, with appropriate randomization in 53 percent (n= 10) of articles^{18,57,64,81,87,97,100,112,120,121} and inappropriate randomization in three (16%).^{17,101,104} The randomization method was not described in six articles (32%).^{10,62,84,95,96,102} Double-blinding was not possible due to the nature of the interventions. All articles reported the inclusion/exclusion criteria, and all but three (84%)^{17,102,104} described the statistical methods used (Figure 14).

Issues with risk of bias in the RCTs included: a lack of reporting on withdrawals: (n=13, 68%),^{10,17,18,62,84,95,97,101,102,104,112,120,121} no description of methods to assess adverse effects (n=18, 95%);^{10,17,18,57,62,81,84,87,95-97,100-102,104,112,120,121} inadequate concealment of allocation (n=13, 68%);^{10,17,62,84,87,95-97,100,101,104,112,120} analysis not based on intention-to-treat principle (n=9, 47%);^{10,17,62,84,87,95-97,112} and inadequate justification of sample size (n=13, 68%).^{10,17,62,81,84,87,95-97,100,102,104,121}

Figure 14. Distribution of risk of bias scores of randomized controlled trials for the psychological and behavioral category (n=19)



Results for Psychological/Behavioral Interventions by Outcome

Tinnitus-Specific Quality of Life

Fifteen RCT studies with WLCs investigated the effects of 27 interventions on tinnitus-specific measures related to quality of life (TSQoL).^{10,17,18,57,62,84,87,95-97,100,102,104,112,120} See Table 23 and Table 24, and Appendix E, Table E4.

The primary measures used to evaluate this outcome included: TRQ,^{57,84,95,96,100,104} TQ,^{17,18,112} THI,¹²⁰ TSI,⁹⁷ TBF-12,⁸⁷ TQ-PI,¹⁰² and other single self-report items.^{10,62} A variety of measures were also tested in addition to these primary measures.

Ten RCT studies with inactive controls evaluated the effect of 13 interventions in the CBT category on TSQoL outcome measures. The TRQ questionnaire was used to measure tinnitus-specific outcomes in five studies in the CBT category which investigated six interventions.^{57,84,95,96,100} A significant reduction in distress due to tinnitus was reported in a study in which CBT was delivered by internet⁵⁷ (group effect on pre- vs. post-treatment change score: $t(70)=3.99$, $p=0.002$); however, when drop-outs were included in an intention-to-treat analysis there was no longer a significant effect. A significant effect in favor of treatment was also reported in a study in which elderly people received six weekly 2-hour group CBT sessions ($F(1,21)=6.4$, $p=0.02$).⁸⁴ A study of two types of cognitive intervention, CR and ACI delivered either alone or together⁹⁶ reported significant reductions in tinnitus distress for the CR, ACI and combined CR plus ACI interventions compared to the WLC ($F(1,46)=6.11$, $p < 0.05$), but significantly more benefit was found when the intervention components were combined than when they were delivered alone. A study comparing a wait list group to two treatments, a cognitive coping training combined with education and an education alone treatment,⁹⁵ reported a significant reduction in tinnitus distress which was significantly greater when the cognitive coping training was combined with education than when education alone was provided ($F(1,57)=16.19$, $p < 0.01$). Finally, a significant reduction in tinnitus distress measured with the TRQ was found for the treatment involving a self-help book and telephone therapy¹⁰⁰ (group x time interaction: ($F(1,70)=12.4$, $p < 0.001$). The TQ was used as the outcome measure in four studies^{17,18,102,112} of five interventions in the CBT category. A study¹⁰² comparing a WLC group

to those who received TCT (TCT1 and TCT2 were delivered by different clinicians) reported that TCT significantly reduced psychological impairment due to tinnitus as measured with a German version of the TQ ($F(1,32)=4.43$, $p \leq 0.04$). In another study comparing TQ outcomes for a WLC group to a group receiving cognitive behavioral TCT intervention,¹⁷ significant effects in favor of treatment were reported ($F(1,34)=9.22$, $p < 0.01$). A psychophysiological CBT intervention¹¹² yielded a significant reduction in tinnitus distress on the TQ in comparison to the WLC group (group x time interaction: $F(1,41)=6.74$, $p < 0.05$, $g=0.64$), as did a biofeedback-based CBT intervention¹⁸ ($F(1,109)=55.40$, $p < 0.001$, $g=1.15$). A significant reduction in tinnitus handicap as measured using the THI was reported in a study in which ACT was compared to a WLC group¹²⁰ (group x time interaction: $F(1,42)=12.16$, $p=0.001$).

Two RCT studies with inactive controls evaluated the effect of three interventions involving TRT on tinnitus-specific handicap using the THI or severity using the TSI. Compared to a WLC group, TRT did not yield a significant improvement on the THI immediately post-treatment in one study.¹²⁰ In the other study,⁹⁷ a group counseling intervention based on TRT principles was compared to a WLC and to traditional group support using the TSI;⁹⁷ significant group effects were not found at the 1-month followup, but the study reported a significant pre- vs. post-treatment improvement on the TSI for the counseling intervention based on TRT and at the 6-month and 1-year followup the counseling intervention yielded significantly greater improvements compared to either the WLC or the support group.

Three RCT studies evaluated the effect on TSQoL for six interventions involving relaxation.^{10,17,62} A significant effect of treatment on the TDI was reported for a minimal contact relaxation intervention compared to the WLC group ($F(1,34)=6.79$, $p < 0.01$), but not on the TQ.¹⁷ For the other interventions involving relaxation, tinnitus-specific outcomes were measured by a single self-report item. In one study,¹⁰ a VAS 'direct' form (10-cm line with end-points labeled 'none' and 'maximum') was completed four times each day with a tinnitus discomfort/annoyance rating item pertaining to the last half-hour and a second retrospective form completed in the evening with a discomfort/annoyance rating item pertaining to the participant's experience over the course of the day (with end points labeled 'absent/very weak' and 'very loud/maximal'). A significant effect on both direct (group x time interaction: $F(1,21)=6.01$, $p < 0.05$) and retrospective measures (group x time interaction: $F(1,21)=7.92$, $p < 0.01$) was reported for a 10-week treatment consisting of training in relaxation, self-control by distraction, and how to apply these methods in everyday situations.¹⁰ In another study,⁶² no effect of a relaxation intervention, delivered with either neutral or counter-demand instructions to two different groups, was found when the extent to which tinnitus interfered with daily activities was measured using one item with a 4-point scale on a monitoring form that was completed daily for a 2-week period.⁶²

Six RCT studies evaluated the effect of other psychological behavioral interventions compared to an inactive control on TSQoL.^{17,87,95,97,102,104} One study⁸⁷ reported that Qigong (mindful exercise) significantly reduced tinnitus handicap as measured using the TBF-12 (a German version of the THI) (group x time interaction: $F(3,66)=3.7$, $p=0.015$). In another study,¹⁰² psychological impairment due to tinnitus measured with a German version of the TQ was not reduced by a yoga intervention. In a study comparing the TQ scores for a WLC group to a group receiving a minimal educational intervention,¹⁷ no significant effect in favor of treatment were reported. As mentioned above, one study⁹⁵ evaluated the effect of CBT combined with education and an education alone intervention compared to a WLC on TRQ score and did not find a significant effect of the education alone treatment. One study evaluated the effect of treatment on tinnitus distress using the TRQ comparing a WLC to bibliotherapy¹⁰⁴ and a

significant reduction in tinnitus distress was found ($F(1,122)=6.23$, $p=.01$, $d=0.28$), but there was no significant effect when an intention-to-treat analysis was conducted for the bibliotherapy intervention.¹⁰⁴ Finally, a traditional support group did not differ from the inactive control.⁹⁷

As seen in the forest plots (Figure 15), almost all of the interventions tended to result in mean effects in favor of treatment. However, only the studies that had group sample sizes greater than 20^{17,18,57,97,100,104,112,120} showed results that could be considered to be significantly in favor of treatment in comparison to an inactive control group. Such positive effects were observed for a number of interventions in the CBT sub-category, including biofeedback-based CBT,¹⁸ psychophysiological CBT,¹¹² internet CBT,⁵⁷ cognitive TCT,¹⁷ self-help book with telephone therapy,¹⁰⁰ and ACT,¹²⁰ as well as one intervention in each of the other sub-categories, including group education with TRT principles,⁹⁷ minimal contact relaxation¹⁷ and bibliotherapy.¹⁰⁴

Strength of Evidence—Tinnitus-Specific Quality of Life

There is low quality evidence (10 studies, 498 participants)^{17,18,57,84,95,96,100,102,112,120} that CBT interventions improve TSQoL when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. Only two studies had a sample size greater than 30 subjects per group and as such, the majority of studies had small sample sizes and lack of power calculations; these studies were judged to be relatively imprecise for this reason. The direction of effect was judged to be consistent across studies showing that the findings favored the CBT treatments; half the studies^{18,57,100,112,120} showed statistically significant differences relative to inactive controls. The confidence intervals had substantial overlap across studies and the magnitude of the effect size was generally greater than 0.5 (medium to large effect) with the exception of three studies.^{95,96,102} Although we judged the directness of these studies to be acceptable, we note that there was marked differences in the types of CBT interventions with respect to the different components and dose administered. Risk of bias was categorized as high, as few studies achieved a score greater than 7 from 12. No dose response pattern was observed. Risk of publication bias is assumed to be high given the small sample sizes of the studies. The SOE for CBT interventions for the outcome of TSQoL is rated as low quality, as the criteria for two domains were not met (Table 25).

There is insufficient evidence (two studies, 182 participants) that TRT related interventions improve TSQoL when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. Both TRT therapy studies favored treatment, but only one was statistically significant; in this study, the sample size exceeded 30 subjects per group. The confidence intervals overlapped to a large degree, but the magnitude of the effect varied from small to medium. Given the difference in effect sizes these few studies were considered inconsistent. One study had a small sample size¹²⁰ and given the lack of power calculations, these studies were considered imprecise. No dose response pattern was observed. Risk of publication bias was rated as high for both studies. The SOE for TRT interventions for the outcome of TSQoL is rated as insufficient as the criteria for three or more domains were not met.

There is insufficient evidence (three studies, 104 participants) that relaxation therapy interventions improve TSQoL when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. The studies were at high risk of bias and showed wide confidence intervals suggesting imprecision (none of the studies had greater than 30 subjects per group). All but one study favored relaxation therapy relative to inactive control, but only one study was statistically significant. The effect size magnitude varied from small to large and as such, these studies were rated as inconsistent. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE

for relaxation therapy for the outcome of TSQoL is rated as insufficient, as the criteria for three domains were not met.

When considering the interventions grouped in the ‘other’ category (six studies, 398 participants, six different interventions), the evidence was deemed insufficient given the heterogeneity of the interventions, the high risk of bias, and small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes within the single studies for each intervention type.

Overall, it seems that there is low quality evidence that CBT interventions have a beneficial effect on TSQoL relative to inactive controls as the criteria for two domains were not met. The other interventions are rated as insufficient SOE as the criteria for at least three domains were not met (Table 26).

Table 25. Strength of evidence by psychological and behavioral interventions in the treatment of tinnitus for the outcome of tinnitus-specific quality of life

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
CBT/CBT combination vs. WLC or no treatment	N/A	10 ^{17,18,57,84,95,96,100,102,112,120}	High	Consistent	Direct	Imprecise	-1.56 (-1.98,-1.13) to -0.13 (-0.93, 0.67)	Low
TRT vs. WLC or no treatment	N/A	2 ^{97,120}	High	Inconsistent	Direct	Imprecise	-0.60 (0-0.93,-0.26) to -0.12 (-0.46, 0.23)	Insufficient
Relaxation vs. WLC	N/A	3 ^{10,17,62}	High	Inconsistent	Direct	Imprecise	-1.02 (-2.20, 0.17) to 0.17 (-1.02, 1.36)	Insufficient
Other psych/behavioral	MC-E vs. WLC	1 ¹⁷	High	Unknown	Direct	Imprecise	-0.38 (-1.05, 0.28)	Insufficient
	BLT vs. WLC	1 ¹⁰⁴	High	Unknown	Direct	Imprecise	-0.33 (-0.68, 0.02)	Insufficient
	Qigong training vs. WLC	1 ⁸⁷	High	Unknown	Direct	Imprecise	-0.14 (-0.82, 0.54)	Insufficient
	Yoga vs. WLC	1 ¹⁰²	High	Unknown	Direct	Imprecise	-0.17 (-0.96, 0.63)	Insufficient

Abbreviations: ACT = acceptance and commitment therapy; BLT = bibliotherapy; BPT = brief phone therapy; CBT = cognitive behavioral training; CI = confidence interval; MC-E = minimal contact education; n = sample size; psych = psychological; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Subjective Loudness

Eight RCT studies with WLCs investigated the effects of 16 interventions on the subjective loudness of tinnitus.^{10,17,18,62,95,100,102,112} See Table 23.

In all studies, subjective loudness was measured on a single item presented using a variety of self-report measures that were administered over a number of days during pre- and post-treatment monitoring periods. These measures included a daily diary entry for 1 week using a 10-point VAS to rate loudness,^{18,100,112} a loudness rating item with a 4-point scale on a monitoring form that was completed daily for a 1-week period⁹⁵ or a 2-week period,⁶² a daily diary entry

(scale unspecified) completed over a two-week period,¹⁷ a VAS ‘direct’ form (10-cm line with end-points labeled ‘none’ and ‘maximum’) that was completed four times each day with an loudness rating item pertaining to the immediate moment and a second retrospective form completed in the evening with a loudness rating item pertaining to the participant’s experience over the course of the day (with end points labeled ‘absent/very weak’ and ‘very loud/maximal’),¹⁰ and a VAS 10-point scale with a loudness rating item that was completed three times per day over a 2-week monitoring period.¹⁰²

The effect on loudness was evaluated for seven interventions in the CBT category. A significant beneficial effect of biofeedback-based CBT¹⁸ was reported (group x time interaction: $F(1,109) = 10.83, p < 0.001$) and a significant effect of treatment on subjective loudness was reported for an intervention using a self-help book with telephone therapy (group x time interaction: $F(1,69) = 6.7, p = 0.012$). No significant effects of treatment on subjective loudness were reported for the other interventions in this category, including internet CBT,⁵⁷ psychophysiological therapy,¹¹² a CBT plus education intervention,⁹⁵ a CBT plus TCT intervention,¹⁷ and a TCT intervention delivered by two different clinicians.¹⁰²

The effect on loudness was evaluated for six interventions involving relaxation that were investigated in three studies with sample sizes of less than 20 per group.^{10,17,62} A significant effect on subjective loudness on both direct (group x time interaction: $F(1,21) = 7.03, p < 0.01$) and retrospective measures (group x time interaction: $F(1,21) = 5.35, p < 0.05$) was reported for a 10-week treatment consisting training in relaxation, self-control by distraction, and how to apply these methods in everyday situations.¹⁰ No significant effect of treatment on subjective loudness was reported for the other treatments in this category, including a minimal contact relaxation intervention,¹⁷ and relaxation delivered with either neutral or counter-demand instructions to two different groups.⁶²

The effect of loudness on three other psychological behavioral interventions was examined.^{17,95,112} No significant effects of treatment were reported for education interventions^{17,95} or for yoga.¹⁰²

The forest plot (Figure 16) for subjective loudness as an outcome of treatment indicates that biofeedback-based CBT¹⁸ and intervention using a self-help book with telephone therapy¹⁰⁰ show beneficial effects of treatment. However, the other interventions, all of which were evaluated in treatment groups with a sample size below 30, did not significantly reduce subjective loudness.

Strength of Evidence—Subjective Loudness

There is low quality evidence (seven studies, 462 participants) that CBT interventions had no effect on subjective loudness when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. For these CBT interventions, only two studies had a sample size greater than 30 subjects per group. Since the majority of studies had small sample sizes and lack of power calculations, these studies were judged to be relatively imprecise. The direction of effect was judged to be consistent as the point estimates in five studies were on the line of no effect. Two studies favored CBT intervention and were statistically significant.^{18,100} With the exception of these two studies, which had large effect sizes, the magnitude of effect was small. Overall these seven studies were judged relatively consistent (overlap of confidence intervals) for subjective loudness. The studies were categorized as high risk of bias with few studies achieving a score greater than 7 from 12. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for CBT interventions for the outcome of loudness is rated as low SOE as the criteria for two of the domains were not met (Table 26).

There is insufficient evidence (three studies, 104 participants) that relaxation therapy interventions improve subjective loudness when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. All of the studies were at high risk of bias. The sample sizes were less than 30 per group, and the effect size estimates showed wider confidence intervals suggesting imprecision. All but one study favored relaxation therapy relative to inactive control and one study favored control; none of the studies showed statistically significant differences between groups. The effect size magnitude varied from small to large, as such, this evidence was rated as inconsistent. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for relaxation therapy for the outcome of loudness is rated as insufficient as the criteria for three domains were not met.

When considering the interventions grouped in the “other category”, the evidence was deemed insufficient given the diversity of interventions, the high risk of bias, and the small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes of the study and the single studies for each intervention type.

Overall, it seems that there is low quality evidence that CBT interventions have no effect on subjective loudness relative to inactive controls as the criteria for two domains were not met. The other interventions are rated as insufficient SOE as the criteria for at least three domains were not met (Table 26).

Table 26. Strength of evidence by psychological and behavioral interventions in the treatment of tinnitus for the outcome of subjective loudness

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
CBT/ CBT combination vs. WLC or no treatment	N/A	7 ^{17,18,57,95,100,102,112}	High	Consistent	Direct	Imprecise	-0.72 (-1.10,-0.33) to 0.01 (-0.61, 0.63)	Low
Relaxation vs. WLC	N/A	3 ^{10,17,62}	High	Inconsistent	Direct	Imprecise	-1.16 (-2.65, 0.34) to 0.21 (-0.45, 0.87)	Insufficient
Other psychological	MC-E vs. WLC	1 ¹⁷	High	Unknown	Direct	Imprecise	0.21 (-0.45, 0.87)	Insufficient
	Education vs. WLC	1 ⁹⁵	High	Unknown	Direct	Imprecise	-0.27 (-0.89, 0.35)	Insufficient
	Yoga vs. WLC	1 ¹⁰²	High	Unknown	Direct	Imprecise	-0.06 (-0.86, 0.73)	Insufficient

Abbreviations: ACT = acceptance and commitment therapy; BLT = bibliotherapy; BPT = brief phone therapy; CBT = cognitive behavioral training; CI = confidence interval; MC-E = minimal contact education; n = sample size; psych/behav = psychological/behavioral; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Sleep Disturbance

Five RCT studies with WLCs investigated the effects of interventions on sleep as a secondary outcome measure.^{18,57,100,102,120} See Table 23 and Appendix E, Table E4.

In one study,¹⁸ the effect of a biofeedback-based CBT on sleep was measured using a diary VAS measure as well as the sleep subscale of the TQ; there were 52 participants in the intervention group and 52 participants in the WLC group who later underwent treatment and

completed post-treatment evaluation. Significant improvements due to biofeedback-based CBT were reported (time x group interaction $F(1,109) = 9.93, p=0.01$ on the VAS diary measure and $F(1,109) = 13.78, p=0.001$ on the TQ subscale). Another study of CBT delivered by internet⁵⁷ reported no significant effect of intervention on sleep.

A third study in the CBT sub-category¹⁰² which had a very small sample size (less than 10 per group), the sleep subscale of the TQ was used to evaluate the effectiveness of two treatments compared to a WLC: cognitive behavioral tinnitus coping training (TCT) administered by two clinicians and yoga. There was no significant effect of these treatments on sleep.

In two other studies with small sample sizes (30 or less per group), one investigating TRT and ACT¹²⁰ and the other¹⁰⁰ investigating a self-help book and telephone therapy, the effects of the interventions on sleep were evaluated using the ISI. The studies reported a significant beneficial effect of the self-help book and telephone therapy¹⁰⁰ on sleep (time x group interaction $F(1,69) = 11.2, p < 0.001$), as well as a significant beneficial effect of ACT¹²⁰ on sleep (time x group interaction $F(1,41) = 5.67, p=0.022$), but no significant effect of TRT.

The findings reported in these studies are in general agreement with moderate heterogeneity among outcomes shown in the forest plot (Figure 17). A significant beneficial effect on the VAS measure in favor of treatment for the biofeedback-based CBT¹⁸ and a significant beneficial effect on the ISI of the self-help book with telephone therapy¹⁰⁰ can be seen in the forest plot, as well as a mean effect in favor of treatment for ACT.¹²⁰ No benefit from internet CBT,⁵⁷ TCT,¹⁰² TRT,¹²⁰ or yoga¹⁰² is evident in the forest plots; however, the sample sizes are smaller and the confidence intervals are larger for these treatments than for the biofeedback-based CBT treatment where benefit from treatment is most apparent.

Strength of Evidence—Sleep Disturbance

There is low quality evidence (five studies, 362 participants) that CBT interventions have no effect on sleep disturbance when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. Only two of these studies have sample sizes greater than 30 subjects per group and both showed statistically significant differences between groups and had relatively smaller confidence intervals. The remaining studies had large confidence intervals and very small sample sizes. Overall, these studies were judged to be imprecise. The direction of effect is generally consistent in that all except one study favor treatment; one study arm favors control but is not statistically significant. The CIs have significant overlap and the magnitude of the effect size are small to moderate (-0.20 and -0.70) suggesting large variation in effect size but the direction of effect is consistent in showing benefit; for this reason the studies were judge to be consistent. The studies were categorized as medium risk of bias and only one study⁵⁷ achieved a score greater than 7 from 12. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for CBT interventions for the outcome of sleep disturbance is rated as low quality as the criteria for two of the domains were not met (Table 27).

There is insufficient evidence that TRT interventions (one study, 44 participants) or yoga (one study, 28 participants) improve sleep disturbance when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. For either intervention, the studies show a point estimate favoring control but this was not statistically significant. The study sample sizes are small and both studies were judged as imprecise. These single studies are at high risk of bias and consistency is unknown. No dose response pattern can be assessed and risk of publication bias is high given the small sample sizes. The SOE for TRT and yoga for the outcome sleep disturbance is rated as insufficient, as the criteria for three domains were not met.

Table 27. Strength of evidence by psychological and behavioral interventions in the treatment of tinnitus for the outcome of sleep disturbance

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
CBT/ CBT combination vs. WLC or no treatment	N/A	5 ^{18,57,100,102;} 120	High	Consistent	Direct	Imprecise	-0.70 (-1.08, -0.31) to 0.61 (-0.23, 1.46)	Low
TRT vs. WLC or no treatment	N/A	1 ¹²⁰	High	Unknown	Direct	Imprecise	0.12 (-0.49, 0.72)	Insufficient
Other psych / behavioral	Yoga vs. WLC	1 ¹⁰²	High	unknown	Direct	Imprecise	0.10 (-0.70, 0.89)	Insufficient

Abbreviations: CBT = cognitive behavioral training; CI = confidence interval; n = sample size; psych = psychological; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Anxiety

Five RCT studies^{57,62,84,100,120} evaluated anxiety symptoms as one of the main outcomes^{57,62,84} or as a secondary outcome^{100,120} that was compared to a WLC group (Table 23). The group mean pre-treatment scores on the STAI suggest that the participants had mild levels of anxiety⁶² and results on the HADS-A^{57,84,100,120} suggest that anxiety symptoms were minimal. Indeed, the HADS-A score was used in one study¹⁰⁰ as an eligibility criterion to rule out anxiety as a major problem. Two studies^{57,84} used the ASI as a second measure of anxiety.

No significant improvement due to group CBT was found using either the HADS-A or ASI in a study with a very small sample size.⁸⁴ However, in another study,⁵⁷ significant effects of CBT delivered by internet to a larger sample size were reported when the change scores for the treatment and wait list groups were compared on both the HADS-A and ASI measures ($t(70) = 3.05, p = 0.004$ on HADS-A and $t(70) = 2.48, p = 0.015$ on ASI). In another study,¹⁰⁰ a significant reduction in anxiety on the HADS-A was reported when the treatment was a self-help book with telephone therapy (time x group interaction: $F(1,70) = 10.1, p = 0.002$). Significant improvement on the HADS-A immediately post-treatment was reported in one study for ACT (time x group interaction: $F(1,41) = 4.40, p = 0.042$; Cohen's d effect size = 0.80, 95% CI (0.14-1.42)), but there was no significant effect of TRT on anxiety.¹²⁰ When relaxation therapy was provided with either neutral or counter-demand instructions, no significant effect of treatment on anxiety was found using the STAI.⁶²

As shown in the forest plot (Figure 18), a clear beneficial effect on anxiety was found for the self-help book and telephone therapy,¹⁰⁰ although this study is considered to have a high risk of bias. There also seems to be a moderate beneficial effect of ACT on anxiety,¹²⁰ but this study also has a high risk of bias. CBT delivered over the internet⁵⁷ and CBT delivered to a small group⁸⁴ have mean beneficial effects on anxiety, but these effects are not significant and the studies have moderate risk of bias. Relaxation⁶² and TRT¹²⁰ seem to have little or no beneficial effect on anxiety.

Strength of Evidence—Anxiety Symptoms

Overall, there is low quality evidence (four studies, 211 participants) that CBT interventions have an effect on anxiety symptoms when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. Given that these studies were of small sample size, with wide confidence intervals, they were judged as imprecise. All studies

showed that the point estimates favored treatment, but only one study¹⁰⁰ was statistically significant; this was the only study with a sample size of greater than 30 subjects per group. The magnitude of the effect size is moderate in all studies and the confidence intervals overlapped substantively; as such, these studies were rated as having a consistent effect. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for CBT interventions for the outcome of anxiety symptoms is rated as low because the criteria for two domains were not met (Table 28).

There is insufficient evidence that TRT interventions (one study, 42 participants) or relaxation therapy (one study, 44 participants) improve anxiety symptoms when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. For these single studies the consistency for each intervention is unknown. The studies have wide confidence intervals and very small sample sizes (less than 30 per group) and the effect estimate is judged as imprecise. Dose response cannot be assessed and risk of publication bias is high for these interventions given the small sample sizes. The SOE for TRT and Relaxation therapy interventions for affecting anxiety symptoms is rated as insufficient because the criteria for three domains were not met (Table 28).

Table 28. Strength of evidence by psychological and behavioral interventions in the treatment of tinnitus for the outcome of anxiety symptoms

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
CBT/CBT combination vs. WLC or no treatment	N/A	4 ^{57,84,100,120}	High	Consistent	Direct	Imprecise	-0.61 (-1.08, -0.14) to -0.27 (-0.76, 0.22)	Low
TRT vs. WLC or no treatment	N/A	1 ¹²⁰	High	Unknown	Direct	Imprecise	-0.19 (-0.80, 0.41)	Insufficient
Relaxation vs. WLC	N/A	1 ⁶²	High	Unknown	Direct	Imprecise	-0.08 (-1.26, 1.11) to 0.46 (-0.65, 1.57)	Insufficient

Abbreviations: CBT = cognitive behavioral training; CI = confidence interval; n = sample size; psych = psychological; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Depression Symptoms

Eleven RCT studies^{10,17,18,57,62,84,95,96,100,102,120} investigated the effects of treatments on depression symptoms by comparing treatments to WLCs (Table 23). The BDI was used to measure depression symptoms in four studies,^{18,62,95,96} the HADS-D was used in four studies,^{57,84,100,120} the ADS was used in one study,¹⁷ a retrospective measure was used in one study¹⁰ and the Depressivitäts Skala was used in one study.¹⁰² As well, the ATQ was used as a second measure of depression symptoms in one study.⁹⁶ Note that depression was used as a primary outcome measure in some studies,^{57,62} but in most studies^{10,17,18,84,95,96,100,102,120} it was considered to be only a secondary or general outcome measure not specifically related to tinnitus. Also note that the eligibility criteria for some studies selected for participants who did not have major problems with depression¹⁰⁰ and the mean pre-treatment scores on standardized measures of depression indicated no more than mild depression.

Nine studies tested treatments in the CBT sub-category,^{17,18,57,84,95,96,100,102,120} four using the HADS-D,^{57,84,100,120} three using the BDI,^{18,95,96} one using the ADS¹⁷ and one using the

Depressivitäts Skala to evaluate the same treatment administered by two different clinicians.¹⁰² Some beneficial effects of treatment were reported in five studies^{18,57,96,100,102} and no significant effects were reported in the other four.^{17,84,95,120}

The four CBT interventions that evaluated depression using the HADS-D included one CBT intervention with six weekly group sessions for adults 65 years of age and older that was compared to a WLC group who later received a shorter version of the treatment,⁸⁴ and an internet-based CBT intervention with six self-help modules that was compared to a WLC.⁵⁷ For the treatment provided to older adults,⁸⁴ there was no effect on depression measured, whereas for the internet intervention,⁵⁷ there was significantly greater improvement for the treatment group compared to the control group for pre-post ($t(70)=3.14$, $p=0.002$) and for pre-followup at 1 year ($F(1,94)=5.4$, $p=0.02$). One study¹⁰⁰ used the HADS-D to investigate the effect on depression symptoms of a treatment involving a self-help book and telephone therapy and a significant beneficial effect was found (time x group interaction; $F(1,70)=5.3$, $p=0.024$). Finally, one study used the HADS-D to evaluate the effect of ACT and found no significant benefit of treatment.¹²⁰

The effects on depression as measured with the BDI were studied in three studies in the CBT sub-category:^{18,95,96} one CBT intervention consisted of eight weekly sessions involving attention control and imagery and cognitive restructuring (ACI + CR) compared to an ACI-only treatment, a CR-only treatment and a WLC,⁹⁶ another CBT intervention was a 12-session biofeedback-based CBT delivered over 3 months compared to a WLC,¹⁸ and a third CBT intervention was a 6-week intervention involving cognitive coping skills training (attention diversion, imagery training and thought management) that was compared to an education only treatment and a WLC.⁹⁵ In the study comparing ACI and CR treatments alone and in combination, it was reported that those who received treatment improved more than the WLC group ($F(1,46)=7.28$, $p<0.01$);⁹⁶ as seen in the forest plot, the benefits of treatment reached significance for the CR plus ACI treatment and the CR alone treatment, but not for the ACI treatment alone. Biofeedback-based CBT resulted in medium pre-post, but only small pre-followup effect sizes and the small improvements in BDI compared to the WLC did not reach significance in the intention-to-treat analysis.¹⁸ There was no significant effect on depression of the cognitive coping skills or education treatments on depression symptoms.⁹⁵

The ADS, a German version of the CES-D designed to evaluate the effect on depression symptoms of an 11-session CBT Tinnitus Coping Training (TCT) group intervention was compared to a WLC as well as two minimal contact (MC) interventions, one entailing two group sessions focused on education about tinnitus (MC-E) and the other group sessions focused on education and music-supported relaxation.¹⁷ There was no effect of treatment on depression and the absence of an effect was attributed to the low levels of depression found at baseline.

The Depressivitäts Skala was used to evaluate the effect on depression when TCT was delivered by two different clinicians compared to a WLC and to yoga.¹⁰² Although one of the TCT groups showed a significant reduction in depression, there was no significant effect on depression reported for the second TCT group or for the yoga group.

The effect of TRT on depression symptoms was evaluated in one study,¹²⁰ and no significant effects were found.

Three interventions focused on relaxation were evaluated: one treatment was the music-supported relaxation intervention that was compared to CBT,¹⁷ one involved relaxation with neutral or counter-demand instructions with each version of the treatment delivered to two groups or stages,⁶² and the third was a treatment emphasizing coping through the use of relaxation and distraction techniques.¹⁰ There was no significant effect of the music-supported

relaxation as measured with the ADS.¹⁷ For the relaxation intervention with different instructions, the only significant effect reported was pre- to post-treatment improvement on BDI (overall pre-treatment mean 12.2 to overall post-treatment mean 8.3), but each group has less than ten participants and this small difference was observed for both the treatment and WLC groups. For the study using relaxation and distraction to enable coping,¹⁰ depression symptoms were measured using a VAS whereby participants marked a 10cm line (from 'none' to 'maximal') at the end of the day for periods of 4 weeks pre- and post-treatment. A statistically significant difference between pre- and post-treatment was reported ($t(20)=2.90$, $p < 0.01$) as well as a small difference between the treatment and control groups that favored the treatment group ($F(1,21)=4.76$, $p < 0.05$).

Three studies^{17,95,102} investigated the effects of other treatments on depression symptoms. The study already mentioned that investigated the effects of TCT using the ADS also evaluated the effects of education (ME-E) on depression symptoms, with no significant benefit reported.¹⁷ The study already mentioned that used the BDI to investigate the effects on depression symptoms of CBT with education also evaluated the effects of education alone and found no significant benefit.⁹⁵ As mentioned above, no significant effect of yoga on depression symptoms was reported.¹⁰² The forest plots (see Figure 19) are consistent with the findings reported in the studies regarding the effect of the treatments on depression symptoms. Overall, less than half of the treatments yielded a significant effect in favor of the treatment in comparison to a WLC.

Strength of Evidence—Depression Symptoms

There is low quality evidence (ten studies, 550 participants) that CBT interventions had no effect on depression symptoms when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. Only two studies had a sample size greater than 30 subjects per group. As such, the majority of studies had small sample sizes and lack of power calculations, and were judged to be imprecise. The direction of effect was consistent across studies showing that the findings favored the CBT treatment in all studies; however, only two studies^{96,100} showed statistically significant differences. The confidence intervals had substantive overlap and the magnitude of the effect size varied. With respect to risk of bias, the studies were categorized as high risk of bias with few studies achieving a score greater than 7 from 12. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for CBT interventions for the outcome of depression symptoms is rated as low quality evidence as the criteria for two domains were not met (Table 29).

There is insufficient evidence that TRT interventions (one study, 42 participants) improve depression symptoms when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. This single study is at high risk of bias and the consistency is unknown. The study had a small sample size (less than 30 per group) and was considered imprecise. Dose response cannot be assessed and risk of publication bias is high for these interventions given the small sample sizes. The SOE for TRT interventions for affecting depression symptoms is rated as insufficient because the criteria for three domains were not met (Table 28).

There is insufficient evidence that relaxation therapies (three studies, 104 participants) improve depression symptoms when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. All three studies favored treatment but none were statistically significant. The confidence intervals overlapped to a large degree but the magnitude of the effect varied from small to large; as such these studies were judged to be inconsistent. The confidence intervals were widely varying and the sample sizes were very small

in these studies, earning a rating of imprecise. All the studies were at high risk of bias. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for relaxation interventions for the outcome of depression symptoms is rated as insufficient as the criteria for three domains were not met.

There is insufficient evidence that MC education (one study, 36 participants), education (one study, 40 participants), or yoga (one study, 28 participants) improves depression symptoms when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. When considering the three interventions grouped in the “other category”, the evidence was deemed insufficient given the high risk of bias for the studies, unknown consistency, and small sample sizes of less than 30 per group (imprecision). Risk of publication bias is high for these interventions given the small sample sizes and the single studies within this group. The SOE for MC education, education and yoga interventions for the outcome of depression symptoms is rated as insufficient as the criteria for three domains were not met.

Table 29. Strength of evidence by psychological and behavioral interventions in the treatment of tinnitus for the outcome of depression symptoms

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
CBT/ CBT combination vs. WLC or no treatment	N/A	9 ^{17,18,57,84,95,96,100,102,120}	High	Consistent	Direct	Imprecise	-1.05 (-1.92, -0.19) to -0.04 (-0.57, 0.49)	Low
TRT vs. WLC or no treatment	N/A	1 ¹²⁰	High	Unknown	Direct	Imprecise	0.05 (-0.55, 0.66)	Insufficient
Relaxation vs. WLC	N/A	3 ^{10,17,62}	High	Inconsistent	Direct	Imprecise	-1.85 (-3.59, -0.11) to -0.06 (-1.24, 1.13)	Insufficient
	MC-E vs. WLC	1 ¹⁷	High	Unknown	Direct	Imprecise	-0.31 (-0.97, 0.35)	Insufficient
	Education vs. WLC	1 ⁹⁵	High	Unknown	Direct	Imprecise	0.08 (-0.54, 0.70)	Insufficient
	Yoga vs. WLC	1 ¹⁰²	High	Unknown	Direct	Imprecise	-0.32 (-1.12, 0.48)	Insufficient

Abbreviations: CBT = cognitive behavioral training; CI = confidence interval; MC-E = minimal contact education; n = sample size; psych = psychological; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Global Quality of Life

Six RCT studies^{17,18,102,104,112,120} investigated the effects of treatments on non-tinnitus-specific global QoL by comparing treatments to WLCs (Tables 23 and 30, Appendix E, Table E4). A number of different measurement tools were employed across the studies, with some measures being more focused on psychological distress and psychopathology, whereas other measures tapped health-related well-being more broadly. The SCL-90-R was used in two studies to measure ‘general psychopathology’^{17,18} and it was listed as a secondary outcome measure in one of those studies;¹⁸ the GHQ-12 was used in one study¹⁰⁴ to measure general psychological distress; the German Beschwerden-Liste was used to measure various symptoms of well-being in one study;¹⁰² the QoLI was used in one study¹²⁰ as a secondary outcome measure of quality of

life based on responses in six domains; the HRLS was used in one study¹¹² as a secondary measure to assess the importance of and satisfaction with eight health-related issues, with a composite index for health-related life satisfaction.

The effect on global QoL was evaluated for six interventions in the CBT category (Figure 20). A significant effect favoring CBT was found for an intervention using biofeedback-based CBT¹⁸ which was evaluated with the SCL-90-R (group x time interaction: $F(1,109)=7.61, p < 0.01$). No significant effect of treatment was reported for CBT using a psychophysiological approach evaluated with the HRLS.¹¹² CBT with TCT and TCT were evaluated in two studies, one using the SCL-90-R¹⁷ and the other using the Beschwerden-Liste;¹⁰² no significant immediate post-treatment effects between the WLC and the treatment groups were reported in either study. ACT¹²⁰ was evaluated with the QoLI and no benefit was found.

The effect on global quality of life by TRT was evaluated in one study¹²⁰ using the QoLI, but no significant effect of treatment was reported.

The effect on global QoL by a relaxation intervention with minimal contact was evaluated in one study¹⁷ using the SCL-90-R, but no significant effect of treatment was reported.

The effect on global QoL was evaluated for three other psychological behavioral treatments: bibliotherapy with the GHQ-12,¹⁰⁴ education with minimal contact with the SCL-90-R,¹⁷ and yoga with the Beshwerden-Liste.¹⁰² No significant effects of treatment on global QoL were reported for education,¹⁷ or yoga.¹⁰² However, a significant reduction in general stress measured with the GHQ-12 with a small effect size was reported for bibliotherapy.¹⁰⁴

As seen in the forest plot (Figure 20), the two most promising interventions are biofeedback-based CBT and bibliotherapy; however, these were the only two studies with sample sizes greater than 50.^{18,104}

Strength of Evidence—Global QoL

There is low quality evidence (six studies, 313 participants) that CBT interventions had no effect on global QoL when compared with inactive controls for patients with idiopathic tinnitus in the immediate or short term followup. All studies were at high risk of bias. Only one study had a size greater than 30 subjects per group.¹⁸ The majority of studies had small sample sizes and lack of power calculations; these studies were judged to be relatively imprecise for this reason. The direction of effect across studies showed that the findings favored the treatment group (point estimate) except for one study (Figure 20). The confidence intervals had significant overlap and the magnitude of the effect size varied from small to moderate; we rated these studies as consistent. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for CBT interventions for the outcome of global QoL is rated as low quality evidence, as two the criteria for two domains were not met (Table 30).

There is insufficient evidence for TRT interventions (one study, 42 participants), relaxation therapy (one study, 36 participants), and “other category” interventions (bibliotherapy (one study, 127 participants), MC education (one study, 36 participants), yoga (one study, 28 participants)) to assess if global QoL is improved relative to inactive control immediately post treatment or in the short term. All studies were at high risk of bias, had unknown consistency, small sample sizes, and wide confidence intervals, except for one study (127 participants)¹⁰⁴ on bibliotherapy in which the SOE was considered low as it was judged to be precise. Risk of publication bias is high for these studies given the small sample sizes of the study and the single studies within each intervention group (Table 30).

Table 30. Strength of evidence by psychological and behavioral interventions in the treatment of tinnitus for the outcome of global quality of life

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the Effect SMD Range (CI)	SOE
CBT/ CBT combination vs. WLC or no treatment	N/A	5 ^{17,18,102,112,120}	High	Consistent	Direct	Imprecise	0.64 (0.02, 1.26) to -0.06 (-0.59, 0.47)	Low
TRT vs. WLC or no treatment	N/A	1 ¹²⁰	High	Unknown	Direct	Imprecise	0.06 (-0.55, 0.66)	Insufficient
Other	BLT vs. WLC	1 ¹⁰⁴	High	Unknown	Direct	Precise	0.45 (0.1, 0.81)	Low
	MC-E vs. WLC	1 ¹⁷	High	Unknown	Direct	Imprecise	0.32 (-0.35, 0.98)	Insufficient
	Yoga vs. WLC	1 ¹⁰²	High	Unknown	Direct	Imprecise	0.26 (-0.54, 1.05)	Insufficient

Abbreviations: ACT = acceptance and commitment therapy; BLT = bibliotherapy; BPT = brief phone therapy; CBT = cognitive behavioral training; CI = confidence interval; MC-E = minimal contact education; n = sample size; psych/behav = psychological/behavioral; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Figure 15. Studies with inactive comparators that evaluate psychological and behavioral interventions and report tinnitus-specific quality of life outcomes

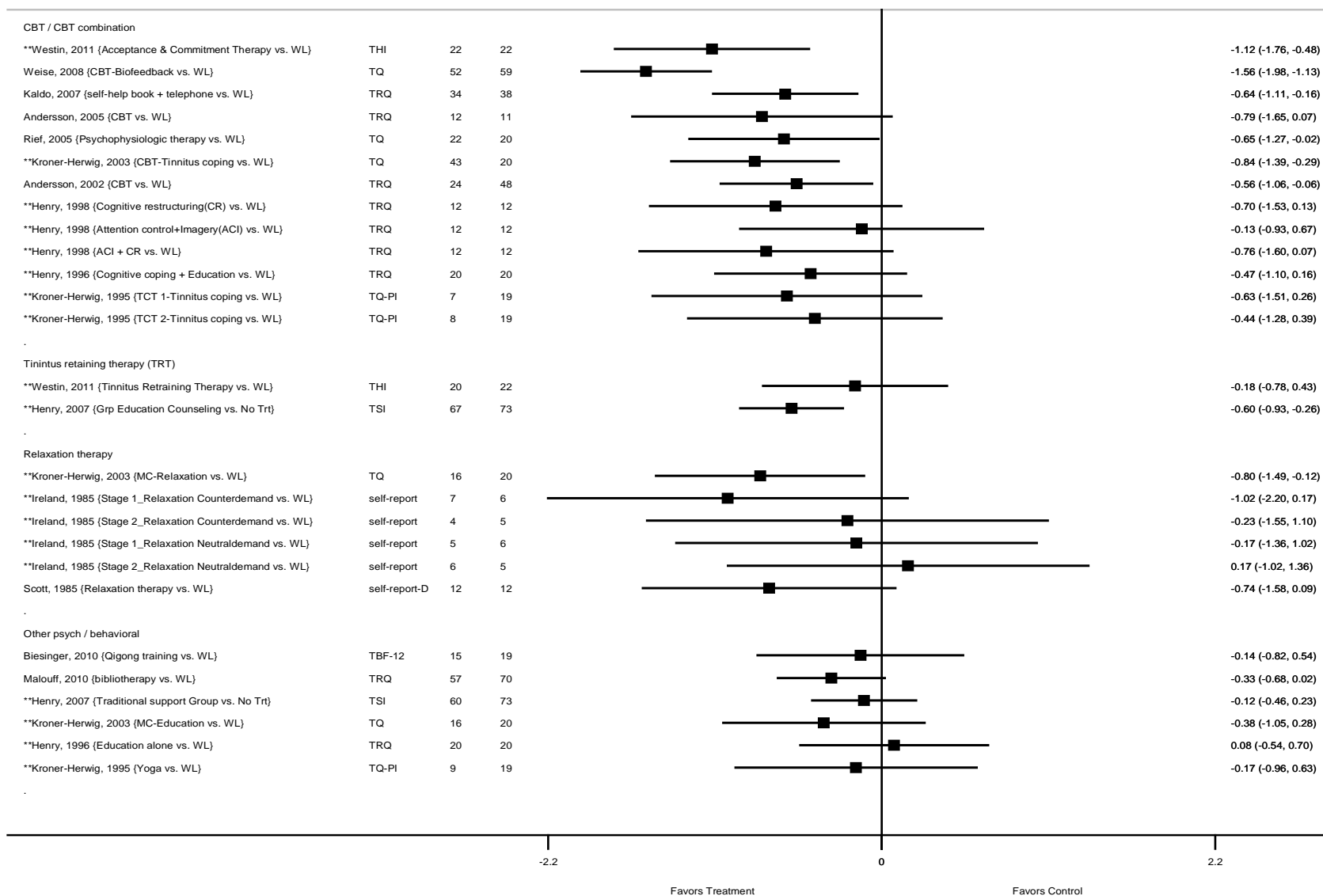
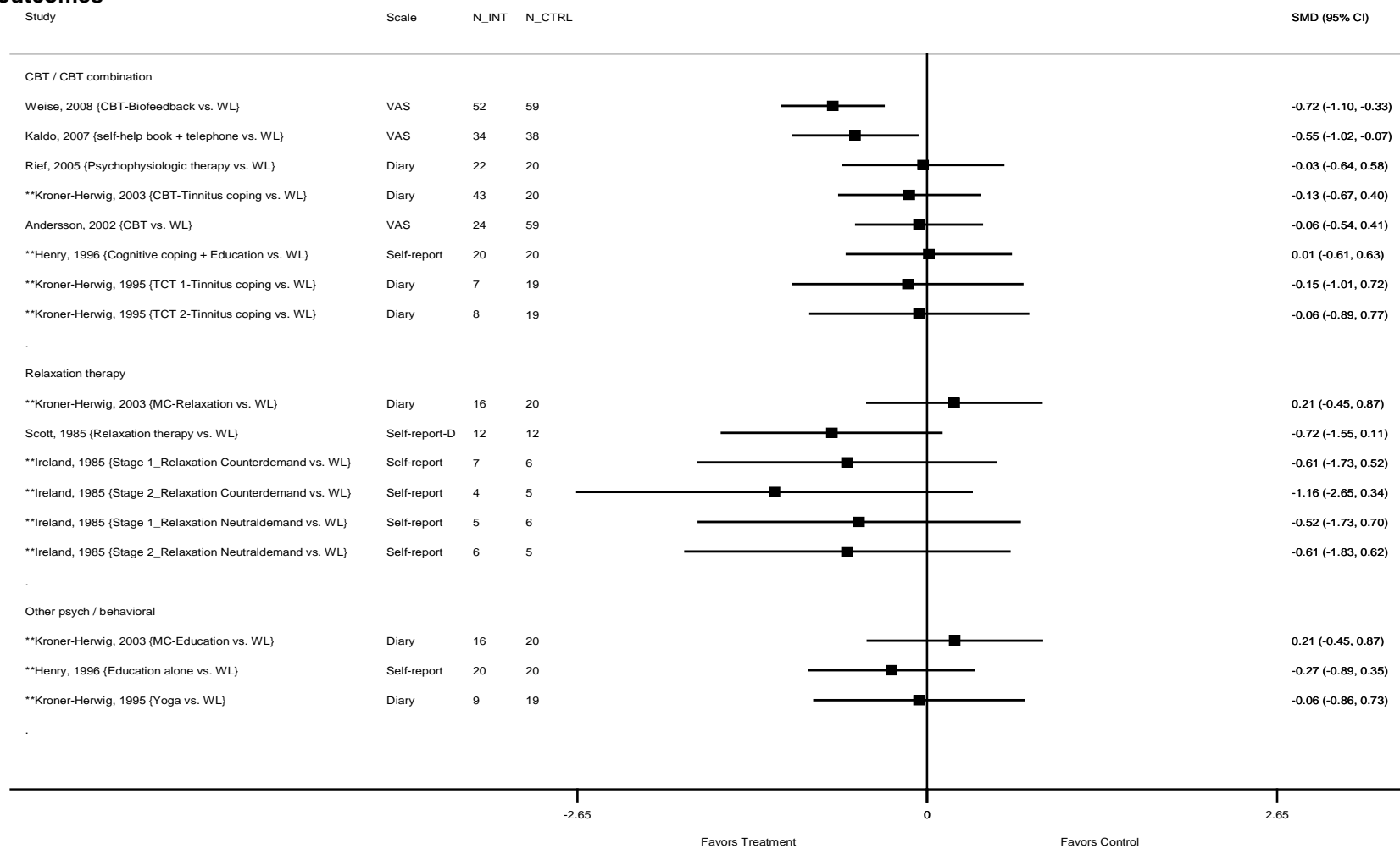


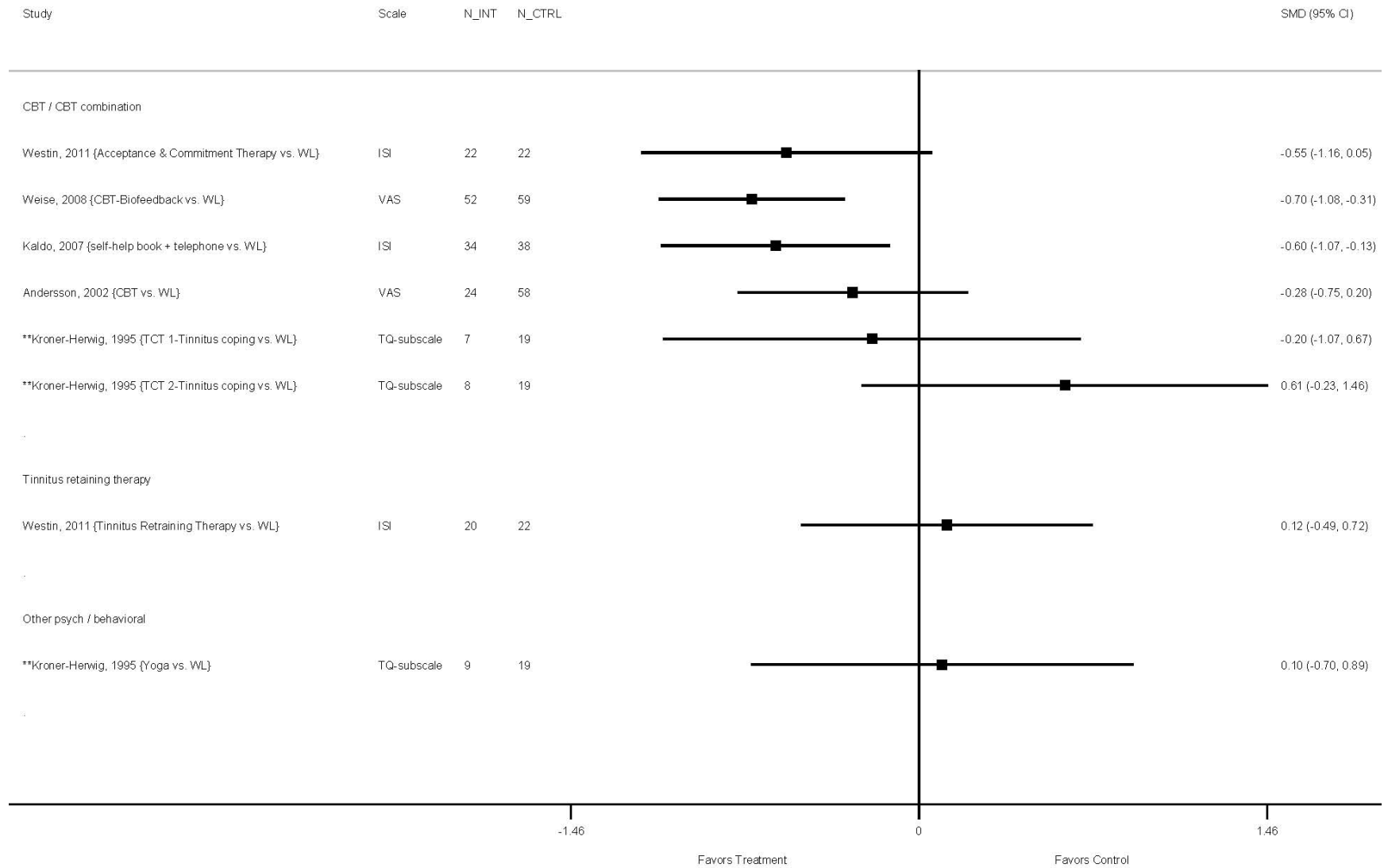
Figure 16. Studies with inactive comparators that evaluate psychological and behavioral interventions and report subjective loudness outcomes



Note: A decrease in score indicates improvement.

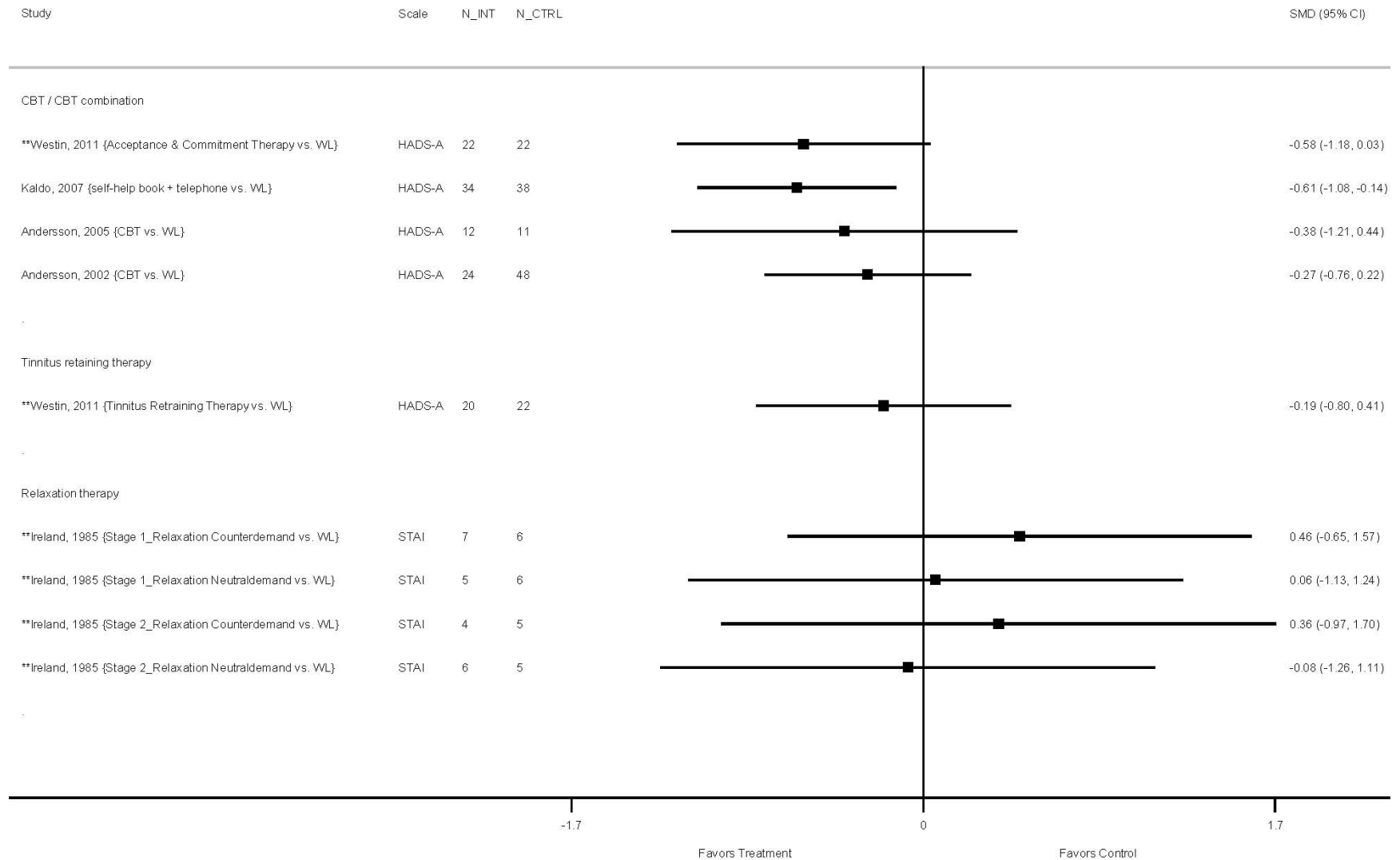
**Represent studies with multiple intervention arms

Figure 17. Studies with inactive comparators that evaluate psychological and behavioral interventions and report sleep disturbance outcomes



Note: A decrease in score indicates improvement.
******Represent studies with multiple intervention arms.

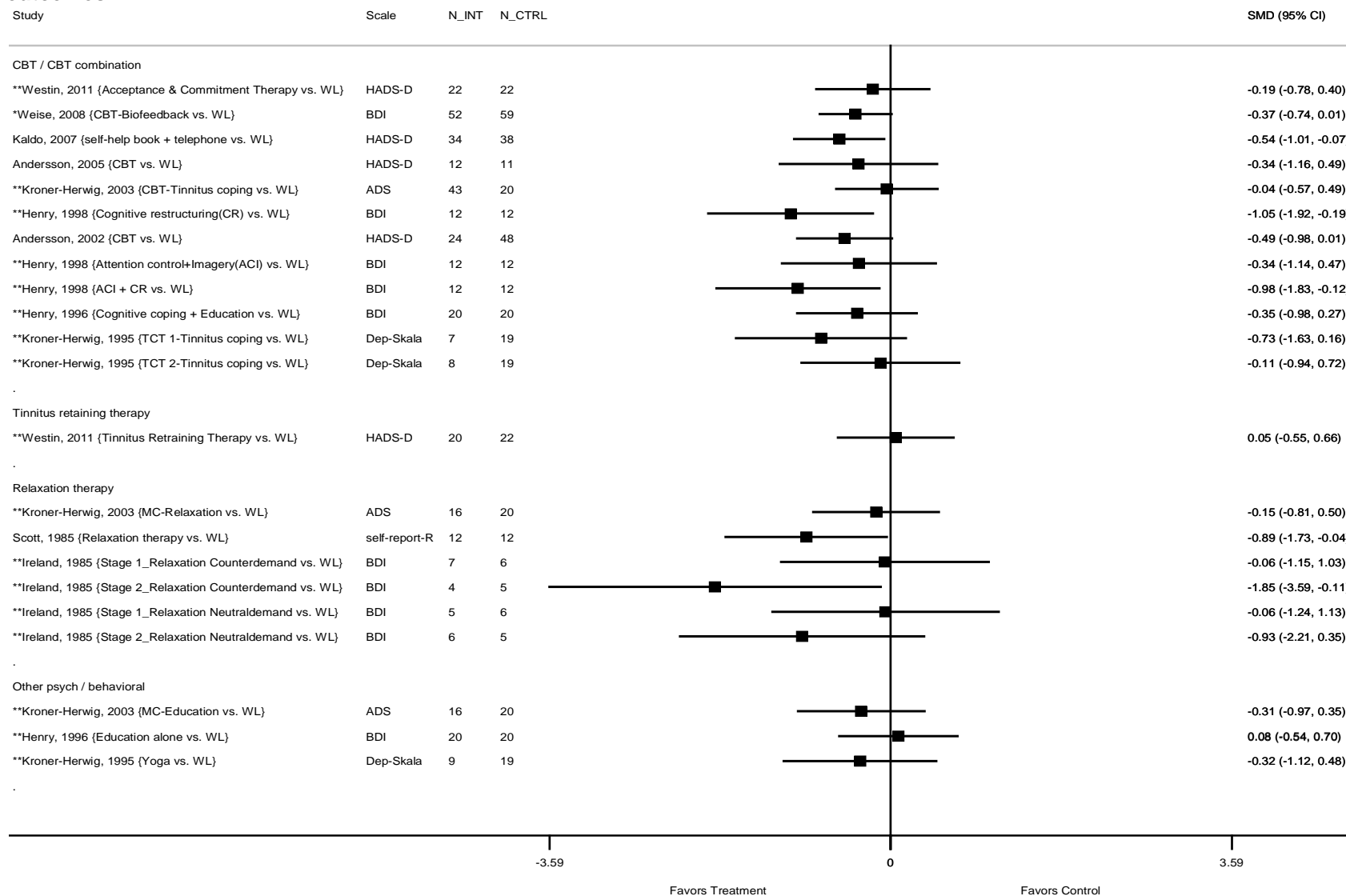
Figure 18. Studies with inactive comparators that evaluate psychological and behavioral interventions and report anxiety symptoms outcomes



Note: A decrease in score indicates improvement.

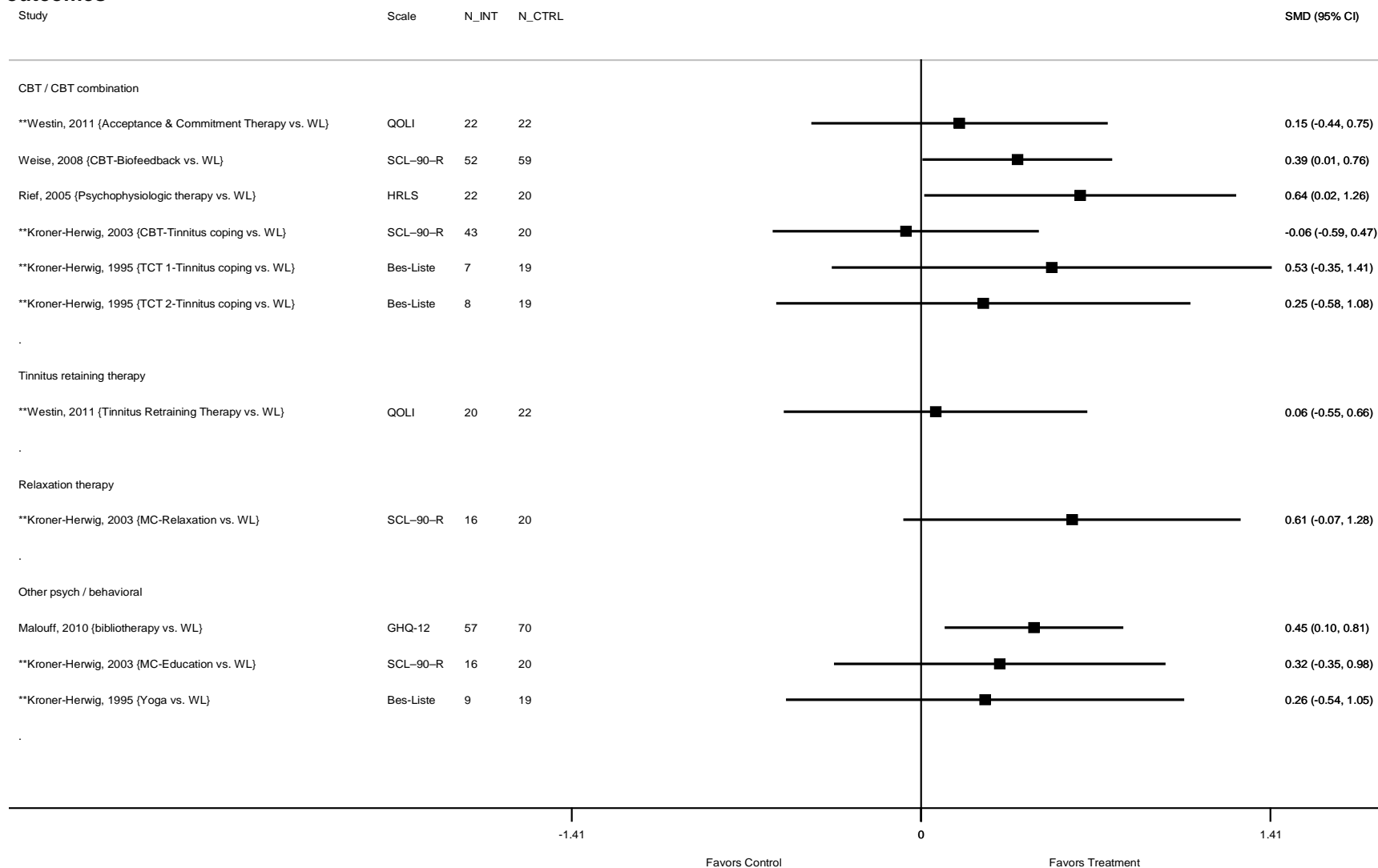
**Represent studies with multiple intervention arms.

Figure 19. Studies with inactive comparators that evaluate psychological and behavioral interventions and report depression symptoms outcomes



Note: A decrease in score indicates improvement.
******Represent studies with multiple intervention arms

Figure 20. Studies with inactive comparators that evaluate psychological and behavioral interventions and report global quality of life outcomes



Note: A decrease in score indicates improvement.
******Represent studies with multiple intervention arms

KQ3. For adults with subjective idiopathic tinnitus, what prognostic factors, patient characteristics, and/or symptom characteristics affect final treatment outcomes?

No data addressing this question were identified in the literature search.

Discussion

Overview

In a rehabilitative context, those with tinnitus are more likely than those without tinnitus to seek professional help and accept hearing aids, presumably because the combination of tinnitus and hearing loss increases disability.^{4,65} However, for the large number of people with hearing loss and tinnitus, typical audiological interventions focus on the remediation of hearing loss rather than on treatments for tinnitus per se.⁴ Tinnitus is a complex condition for which a variety of interventions have been applied. This Comparative Effectiveness Review (CER) attempted to evaluate Key Questions (KQ) 1 and 3 regarding methods to assess different treatment strategies, and possible prognostic factors, related to tinnitus outcomes. Although the search was comprehensive, there was no literature eligible for KQ1 and KQ3, thereby identifying some significant gaps in the literature. For KQ2, which examined treatments for tinnitus, this CER has identified and shown that the strength of evidence (SOE) is generally of low quality, suggesting that the results of these studies do not necessarily reflect the true effect of these interventions and that future research is very likely to change both the direction and magnitude of the effects for these interventions. This evidence review demonstrates the research gaps with respect to KQ1 (methods to identify further evaluation and treatment) and KQ3 (prognostic factors).

A critical discussion for each of the KQ is presented below.

KQ1. In patients with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds) what is the comparative effectiveness of methods used to identify patients for further evaluation or treatment?

The intention of this question was to determine if some methods were more effective than other methods when used by primary care providers or specialists in tinnitus care to determine if a patient with tinnitus should be referred for rehabilitation. Note that the type of tinnitus was not restricted for KQ1. The criteria for including studies allowed methods that involved direct observation or observation of sound with a stethoscope, the administration of scales/questionnaires to assess severity. Importantly, these studies were restricted to primary and specialty care with the specific outcomes of the method establishing any of the following: 1) no treatment necessary; 2) need for specialized treatment; and, 3) extent of intervention. This last criterion was the one that most affected eligibility for this systematic review.

There are several validated questionnaires²³ currently being used for assessing the symptoms and the impact of tinnitus and very recently a new comprehensive instrument, the Tinnitus Functional Index (TFI),²⁶ was developed by consensus among a large number of researchers who had introduced earlier measures. Nevertheless, no research has contrasted one measure with another existing instrument in order to evaluate which was better for addressing candidacy for further treatment or the type and amount of treatment required. Similarly, psychological grading scales, which can help discriminate between clinically significant and non-significant degrees of tinnitus, were not compared directly. Furthermore, the relative suitability of different methods for evaluating candidacy for and likely outcomes of specific treatments has not been studied. Some attributes regarding the potential usefulness of different measures and the criteria for treatment candidacy are suggested in the studies examined in regard to KQ2. Future research in this area is critical in order for the field to move forward.

It is noteworthy that, in parallel with the evolution of behavioral interventions, tinnitus-specific measurement tools have evolved to incorporate more of the psychological aspects of stress/distress with reduced focus on auditory perception. This reflects the historical development and understanding that tinnitus as a symptom is to be managed rather than a disease to be cured. It also highlights the potential problem of comparing studies using different instruments to establish either the candidacy for or the efficacy of treatments when the instruments are based on vastly different assumptions about the nature of the problems associated with tinnitus. Future evidence syntheses will have to judiciously consider the various domains within complex instruments encompassing multiple areas of quality of life or symptoms. Specifically, many of the tinnitus-specific measures (Table 5) include questions concerning multiple outcomes of interest in the present review. It is noteworthy that this dilemma is not unique to the area of tinnitus; efforts to bank individual items rather than summary scores when making outcome comparisons is endemic in rehabilitation areas where disorders are complex. Comparison of findings across studies when outcomes contain different domains and weightings of items within these domains has necessitated consensus work to establish core measures (a minimal set of functions or items) to capture important domains based on the International Classification of Function (ICF) (see example for stroke¹⁴⁸). Note that an ICF core set for hearing has almost been completed (<http://www.icf-research-branch.org/icf-core-sets-projects/other-health-conditions/icf-core-set-for-hearing-loss.html>). Ultimately, it would be useful to develop such a core set for tinnitus and the TFI promises to be an important step in this regard.

KQ2. In adults with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of pharmacological, medical, sound treatment/technological, or psychological/behavioral interventions (including combinations of interventions)?

In general, it is difficult to draw overall conclusions about treatment benefits given the diversity of interventions and outcomes in the studies that satisfied the inclusion criteria for this research question. Studies were heterogeneous in terms of populations, treatments, treatment modalities (e.g., many different types of CBT), study duration and followup periods, and outcome measures. Although we estimated effect sizes using standardized mean differences, they are difficult to interpret. Some interventions did show positive benefits, but it was difficult to judge the degree of clinical significance of the changes across studies. Even if differences in treatment-placebo scale scores were statistically significant, these differences may not be clinically meaningful. Future research must consider pilot work to establish the validity of many of the outcomes used in the studies eligible for this question; moreover, specific adaptations of measures validated in non-tinnitus populations (i.e., study-specific visual analogue scales (VAS) should be established in the tinnitus population, particularly for the attributes of change over time (responsiveness). For some of the tinnitus-specific outcomes, it is critical that clinically important differences be established.

For some interventions (e.g., pharmacological agents, acupuncture, Qigong, etc.), only single studies were evaluated and many of these were very small with respect to sample sizes. One clear trend was that, given their sample sizes, many studies were likely underpowered to detect differences. Thus, there is little or no confidence in the findings of studies that showed no differences relative to placebo or inactive control comparators, and it is prudent to assume that these do not reflect the true effect of the interventions being evaluated.

Perhaps the heterogeneity among studies reflects differing paradigms based on evolving knowledge about the nature of tinnitus. It would be important that future studies designed to evaluate interventions be well grounded in neuroscience and reflect a conceptual framework providing rationales that take into account the auditory, cognitive, emotional, and stress circuits thought to underpin the characteristics of the disorder. It may also turn out that different subtypes of tinnitus will be identified according to whether the main feature of the tinnitus relates to auditory, cognitive, emotional, or other disorders. Recent research findings from cognitive and auditory neuroscience studies have advanced knowledge of the biological mechanisms for some forms of tinnitus, while findings from clinical psychology studies have underscored the interactions among the auditory, cognitive, affective, and mental health issues that must be considered when designing and evaluating interventions to meet the needs of clinical subpopulations of patients.

The perspective brought to this evidence synthesis is that tinnitus is a symptom or condition and not a disease, suggesting that it is multi-factorial and complex. As such, it is not surprising that the focus of interventions is shifting from “curing” tinnitus by trying to mask or eliminate the perception of tinnitus to providing strategies for coping/control/relief. The auditory aspect of tinnitus was an early focus of many of the treatment approaches to manage it, with many of those suffering from tinnitus seeking medical rather than psychological treatments; in contrast, the present understanding of the problem would suggest that the “sound” per se is not the only issue.¹⁸ Rather, the reaction to the sound suggests that it is more than just an auditory problem; tinnitus often entails psychological distress.¹² Nevertheless, new sound generating technologies continue to be developed and tested.¹¹⁶ The implications of this for future research are to continue to broaden baseline assessments and types of outcomes to capture these additional dimensions. A systems approach that addresses the interaction of the auditory, emotional, and cognitive aspects of tinnitus could be considered.

The diversity of interventions and treatments eligible in this review did not provide guidance with respect to the dose of the treatment interventions (for how long and how much) to achieve an acceptable effect. The studies evaluating CBT provide some information about the amount of clinician-patient contact required to achieve statistically significant outcomes; the primary motivation being to design programs that can be self-administered or delivered over the phone or internet in order to improve cost/benefit, accessibility, varying needs of patients, and efficiencies in the allocation of limited clinician resources. Future studies may need to consider earlier phase trial designs to establish adequate doses for the various interventions. Contextual parameters also need to be considered with respect to the setting and the personnel providing the service and what type of specialization is required for the specific intervention.

This review considered adverse effects related to tinnitus symptoms (worsening of tinnitus, sedation symptoms, and surgical complications). From these, the SOE for sedation (drowsiness, excessive sleepiness) could be evaluated and this effect was reported in studies evaluating primarily pharmacological interventions. The evidence was rated as insufficient for the outcome of sedation, due to the diversity of drugs and the few studies that reported this adverse effect. Some of the studies evaluating other pharmacological and medical interventions also attempted to capture and report other types of treatment emergent adverse effects. However, almost none of the psychological behavioral interventions evaluated or reported adverse effects and those that did indicated that there were no adverse effects. In some studies, worsening of tinnitus-related symptoms was noted.⁹² Although, it may be difficult to identify potential unintended effects with these types of psychological and behavioral therapies, it would still be important to consider

what some of these might entail. Whereas patients who see no effect with a medical/surgical intervention, such as a drug, may tend to feel that the medication failed them and not that they failed the medication. In contrast, participants in psychological/behavioral interventions may tend to feel that they failed the psychotherapies. For example, the patient who commits to psychological therapy and then experiences no improvement might tend to be emotionally troubled by this result (if they had tried harder, been more open, done the homework, participated in group more, etc.). In general, it was observed that the majority of studies evaluating these interventions did not adequately identify or collect potential adverse effects. The inability to distinguish whether the studies measured these harms as opposed to simply not reporting them, either because no events occurred or they occurred at the lowest frequencies, makes rating SOE for outcomes of harm problematic.

Future research should adequately capture harms, particularly if head-to-head trials comparing two different treatments are of interest. That is, if there is no meaningful difference in the potential outcomes of benefit, the margins between benefits and harms become narrower. Given that many of the treatments evaluated were likely to have no difference or are potentially equivalent, evaluation of harms takes on a greater importance for judging the relative efficacy of the two interventions.

Trial registries were reviewed to ascertain what future trials are ongoing (Appendix F) and 26 registered trials were found. The largest number of trials are evaluating sound technologies interventions using varied sensory stimulation devices (n=6); additionally, four trials will be evaluating repetitive transcranial magnetic stimulation (rTMS), and two assessing vagal nerve stimulation. Five trials are registered to evaluate pharmacological agents (i.e., cilostazol, NST-001, AM-101, and neramexane mesylate) or food supplements (i.e., magnesium). One trial will compare the efficacy of a behavioral intervention to a pharmacological agent. There are seven trials registered that will evaluate psychological/behavioral interventions. Overall, this reflects significant research activity in interventions aimed at remediating problems associated with subjective idiopathic tinnitus using a wide range of interventions.

Studies Involving Pharmacological and Food Supplement Interventions

A total of 16 unique studies^{28,82,85,86,90,93,106,107,109,111,113-115,117,119,122} evaluated the efficacy of pharmacological interventions or food supplements in tinnitus. The studies examined six outcomes: TSQoL, subjective loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global QoL. Another article⁹⁹ contained additional data to supplement one of the study publications.¹²²

The included studies evaluated 14 different interventions, all but one of which were compared to some form of placebo. In a crossover study,¹⁰⁷ all participants received Deanxit in addition to clonazepam, with the comparator being placebo in addition to clonazepam. The study of honeybee larvae⁸⁵ involved hydrogenated dextrin as the comparator. Authors of the included studies measured outcomes using a multitude of different instruments, ranging from validated scales such as the HAM-D to 10-point or 100-point VAS. For the most part, the interventions failed to demonstrate statistically significant effects compared with placebo on any of the six outcomes. Various interventions did show statistically significant effects on some outcomes: nortriptyline¹¹⁵ and honeybee larvae⁸⁵ for depression; alprazolam²⁸ and zinc⁸⁶ for loudness; and acamprosate⁸² for TSQoL measured as ‘disturbance’. One study¹¹⁵ found conflicting results for tinnitus-specific QoL depending on the outcome measure.

The only intervention that consistently showed statistically significant effects on multiple outcomes was sertraline, which was evaluated against placebo in a 16-week study of 63 persons who had a mean age of 42 years. These persons were recruited from a specialized audiology clinic and given 50 mg/day of the active therapy or placebo. Sertraline was shown to be more efficacious than placebo in reducing loudness, improving global QoL, and alleviating severity. Sertraline also had a greater impact on reducing depression symptoms, although the reduction failed to reach statistical significance at the 5 percent level on one of the three scales used to measure depression.

Several issues must be considered when interpreting the results described above. Although sertraline does appear to have beneficial effects on certain tinnitus outcomes, this medication has only been evaluated in one 2006 study.¹²² More evidence is required prior to drawing firmer conclusions about the drug's usefulness against tinnitus. The same caution is relevant for the other therapies that did not show any benefits against tinnitus. Further research is required for us to assess whether or not these treatments are beneficial for persons with tinnitus.

Thirteen of the 16 studies had sample sizes of less than 100 persons. Most of these papers were bereft of sample size calculations or author commentaries on the adequacy of their sample sizes. This issue raises the question of whether the studies had adequate power to detect statistically significant differences, let alone minimum clinically meaningful differences. Although the three largest studies^{93,109,113} did not find differences between the treatment and placebo groups, these results cannot be used to conclude that the smaller studies would also not have found differences had they employed larger samples. Each of the three large studies evaluated a different active therapy and, in only a single case did a smaller study examine one of the same therapies as in a larger study.^{93,111} Thus, the results of the larger studies are therapy-specific and in no way generalizable to the findings for the other treatments.

The issue of minimum clinically meaningful differences is important when one considers the characteristics of the outcome measurement instruments used in the included studies. Few of the authors commented on the validity of their instruments, both in terms of measuring the outcomes of interest or for assessing these outcomes specifically in persons with tinnitus. Even though some instruments might be suitable measures of tinnitus-specific outcomes (e.g., Tinnitus Handicap Inventory for symptom severity), and other instruments might be valid measures of constructs such as depression (e.g., HAM-D), the authors did not provide details on the minimum changes in instrument scores that would be considered clinically meaningful. For example, the sertraline study¹²² used a 100 mm VAS to measure loudness and the authors reported that the mean change in score between baseline and the end of 16 weeks of followup was 15.21 (standard deviation=20.38) in the treated group and 3.21 (standard deviation=20.91) in the placebo group. For clinicians or persons with tinnitus, does a mean score change of 15.21 indicate that a majority of patients on the active treatment were clinically improved? Also, is the treatment-placebo difference in mean score change at the end of followup (i.e., 12.00) indicative of an important clinical difference between the study groups? The same questions apply to all of the instruments used in the included studies (AS and validated instruments alike). It is recommended that authors justify their choice of outcome measures from the standpoint of validity. Additionally, authors should specify (and justify) the minimum differences in instrument scores that are claimed to be clinically important.

Another important issue to consider is the ability of an instrument to discriminate between treatment effects across study groups (in other words, the ability to detect minimum clinically meaningful differences). Even valid instruments might contain a certain degree of imprecision

that blurs between-group differences. In some cases, the imprecision might be large enough to prevent researchers from detecting true effects. In other cases, the presentation of summary scale scores might obfuscate the imprecision and make the differences between treatments appear larger than in reality. To see an illustration of the latter point, the standard deviations associated with the mean VAS scores in the previous paragraph exceed the mean scores themselves. Assuming the data are normally distributed, a standard deviation of 20.38 for the sertraline group means that 34.1 percent of the 29 persons who received this drug (n~10) actually had a change in score of somewhere between -5.17 (worsening loudness) and 15.21 on the VAS (mean – standard deviation). Also, 15.8 percent (n~4 - 5) had a change in score that was worse than -5.17. For the placebo group, 34.1 percent of the 34 persons who received placebo (n~11 - 12) had changes in score between 3.21 and 24.12 (mean + standard deviation). A further 15.8 percent of the placebo group (n~5) had changes in score that exceeded 24.12. When considered in this fashion, the differences between the active and placebo groups do not appear as great as the means suggest. Authors must carefully consider an discriminative ability of an instrument prior to use in a study. Such consideration will mitigate the potential of a type II error (failing to reject the null hypothesis when it should be rejected) or prevent treatment differences from appearing larger than in reality.

Studies Involving Medical Interventions

Eleven studies evaluated four different types of medical interventions that included rTMS,^{83,88,103,105,110} electromagnetic stimulation,⁹⁴ low level laser therapy (LLLT),^{35,89,108} acoustic coordinated reset neuromodulation (ACRN),¹¹⁶ and acupuncture.¹¹⁸ Almost all studies in this grouping evaluated tinnitus-specific QoL. In general, the SOE for TSQoL is rated as low or insufficient based on the high risk of bias, and the small sample sizes, lack of power calculations, and lack of specification of the primary outcomes are factors related to the imprecise rating. Many of the studies did not show statistical differences between groups, but limited statistical power is likely an important factor.

When considering the individual types of interventions and efficacy with respect to TSQoL, the studies consistently showed no significant difference between treatment and inactive comparators. For rTMS and electromagnetic stimulation the evidence was rated as insufficient. There was some evidence that longer term effects (improvement in TSQoL scores) occurred with low frequency rTMS (1 Hz) up to 6 months followup⁸³ but this single study was at high risk of bias. This review also showed that adverse effects were generally poorly evaluated and reported. A previous systematic review¹⁴⁹ reached similar conclusions suggesting that the evidence of benefit for rTMS is limited; also noted is the lack of long-term monitoring within the studies with respect to safety. Strength of evidence was rated as insufficient for TSQoL with respect to the interventions of ACRN, LLLT, and acupuncture.

When considering the outcome of perceived loudness, there were only five trials that evaluated this outcome^{35,88,108,116,118} and most trials showed no statistical differences between treatment and inactive control groups; however, the studies had small sample sizes and are at high risk of bias. A single study evaluating LLLT relative to sham LLLT evaluated an outcome capturing anxiety symptoms and depression symptoms;¹⁰⁸ this trial was judged to have insufficient SOE. No studies evaluated the effect on sleep disturbance and global QoL with these interventions.

The studies in the medical intervention grouping have relatively small sample sizes (less than 60 subjects total) and none of the studies undertook formal power calculations. As such, type II

error cannot be ruled out. Issues related to statistical power, poor characterization of study participants, and poor study conduct (high risk of bias) all likely contributed to the nonsignificant results observed across the different interventions. Future research should provide a more coherent rationale for the particular treatment approaches based on current neurological science principles, including justification for the dose of the intervention.

Studies Involving Sound Technologies

The idea that external sound can cover up the internally generated sound of tinnitus or that external sound can provide relief or can distract a person's attention away from tinnitus has led to the use of maskers or sound generators for tinnitus. The use of masking became popular over 30 years ago and it has long been observed that people with hearing loss and tinnitus often report relief from tinnitus when hearing aids are worn to amplify external sounds. Nevertheless, only four unique studies^{53,61,92,98} and a related study⁹¹ were eligible for inclusion in this review, all published within the last 15 years. It seems likely that research concerning the effectiveness of early forms of sound technologies predated the use of RCT methodologies. Another possibility is that research to investigate the effectiveness of sound technologies such as hearing aids and cochlear implants in populations with hearing loss, may have included measures of tinnitus relief, but the primary purpose of the research was to investigate benefits in terms of hearing rather than tinnitus outcomes.

It is noteworthy that all of the papers reviewed for this category of intervention were head-to-head trials, possibly also reflecting the relative maturity of sound-based interventions in audiology. Of the studies examined in the present CER, the emphasis was on whether or not the use of noise generators enhanced benefit from psychological/behavioral interventions such as CBT or tinnitus education,⁹⁸ whether using one or another type of sound technology (sound generators vs. open ear hearing aids) for people with mild hearing loss had differential effects on benefit from tinnitus retraining therapy (TRT) counseling,⁶¹ whether benefit from an information intervention was augmented by the addition of a white-noise generator and/or relaxation,⁹² and whether or not benefit depended on the type of stimulation used in Neuromonics Tinnitus Training.⁵³ Benefits from treatment were reported in some studies; specifically, benefit from treatment was reported for TSQoL based on THI scores, subjective tinnitus loudness and global QoL for the TRT interventions with either sound generators or open ear hearing aids⁶¹ and benefit from TSQoL based on TRQ scores was reported for the Neuromonics Tinnitus Training with either type of stimulation.⁵³ However, no study reported any significant difference between the treatments evaluated on any outcome measure.

Similar to the issues raised above for the other interventions, the SOE is limited by relatively small sample sizes of less than 100 per group. In two studies,^{92,98} pre-/post-treatment comparisons were analyzed to establish any benefits from intervention. In all cases the varieties of treatment evaluated were primarily focused on determining whether one or more treatment components enhanced another and the characteristics of the subpopulations tested were usually well defined (e.g., only people with mild hearing loss⁶¹). The comparison of treatment measurement issues are similar and perhaps even more challenging when compared to the issues raised previously regarding the test properties and clinical interpretation of test results when outcomes are measured to evaluate treatments versus an inactive comparator. In general, if the test properties and clinical interpretation of results were refined, then more research is to be encouraged to determine the specific contributions of treatment components for tightly controlled subpopulations. Two recent systematic reviews evaluating a different set of eligible

studies derived a similar conclusion suggesting insufficient evidence⁷ or remarked upon the diversity of interventions and the lack of evidence overall.¹⁵⁰

Studies Involving Psychological/Behavioral Interventions

Similar to the medical interventions, the psychological and behavioral interventions were diverse and a clear overall summary of effects was difficult to ascertain. Even the studies that had similar interventions had marked differences in the focus and administration of the therapy, rendering between-study comparisons problematic. Despite this diversity, this review judged the SOE to be of low strength for CBT and coping approaches, suggesting low level of confidence that the studies evaluating these interventions reflect the true effect for outcomes of importance analyzed (i.e., evidence of benefit for TSQoL and no effect for other outcomes). Two independent systematic reviews and meta-analyses^{55,58} evaluating CBT-based interventions only and with slightly different set of included studies relative to this review, have a beneficial effect on TSQoL measures as compared with active controls. One review⁵⁵ also confirmed these findings with respect to subjective loudness; however differences with respect to CBT therapies positively affecting depression symptoms were determined. Note that the apparent absence of benefits from treatment for outcomes related to anxiety and depression symptoms may not be meaningful given that most of the participants in the studies had no more than mild symptoms pre-treatment. Recent systematic reviews have evaluated TSQoL and CBT interventions and rated the evidence as moderate⁷ or showed evidence of benefit.^{7,55,58,150} This systematic review did not undertake comparisons between studies with inactive and active comparators. Other systematic reviews that have addressed this issue suggest that there is no difference with respect to the comparator group and the efficacy of CBT interventions on TSQoL. One review⁵⁵ included eight studies and three of these had yoga or education as the comparator groups; the other five studies were wait list control. There were no specific conclusions about active versus inactive controls, but for the outcome of quality of life (equivalent to TSQoL in this report) they conclude that the studies with wait list control showed a larger effect size. A second review⁵⁸ performed a subgroup analysis comparing studies with active and inactive controls and only found a trend that analyses of active control conditions (education controls or credible treatment controls) had significantly lower effect sizes than analyses with passive control groups (wait list control). However, CBT compared with a passive and active control at post assessment yielded statistically significant mean effect sizes for tinnitus-specific measures (Hedges's $g=0.70$, and Hedges's $g=0.44$, respectively) based on post treatment means only; this suggests that CBT was effective in both active and inactive comparator studies. Another¹⁵⁰ evaluated 10 RCTs that compared CBT to a non-CBT control, of which nine reported significant improvements in tinnitus intrusiveness. Their findings indicate that this positive effect appears to be independent of whether CBT is compared to an educational or wait list control, suggesting that either measure adequately controls for placebo effects in these studies. Although there were fewer studies using active controls, comparisons in these three other systematic reviews would suggest that the comparator does not affect the main conclusion that CBT interventions appear to improve quality of life relative to both active and inactive controls. One of these previous reviews also suggests that the evidence shows that CBT interventions do not affect depression and anxiety symptoms,¹⁵⁰ and other reviews suggests the evidence demonstrates that CBT improves depression scores⁵⁵ or mood.⁵⁸ One review showed no evidence of CBT affecting subjective loudness.⁵⁵

Behavioral interventions (i.e., relaxation, education, TRT) employed an isolated approach that did not confer the same degree of benefit and were rated insufficient, being plagued with the same problems as the studies evaluating pharmacological and medical interventions. It was observed that CBT combined with other behavioral interventions (e.g., EMG biofeedback¹⁸ in this review) were common treatment options. There has also been a movement attempt to tease apart the active ingredient of some complex interventions or to compare treatments with demonstrated benefit to each other. Two recently published RCTs^{151,152} that were not indexed at the time the databases were searched for this CER illustrate this point. The first report¹⁵¹ showed that both internet CBT and internet ACT yielded equivalent benefit with the conclusion that either are viable treatment alternatives that may be chosen by or for patients. It is interesting that there is active development of progressive^{46,63} or staged treatments,⁶⁴ which could be a promising avenue to further explore in future studies. The second report¹⁵² is an example of a staged treatment study in which benefits on a new measure of tinnitus-specific quality of life were found. The group receiving a psychoeducational intervention, followed by 6 weekly sessions of mindfulness training that emphasized acceptance, showed benefit but the same psychoeducational intervention followed by a relaxation therapy did not. However, trials evaluating complex interventions are problematic if a simple parallel design is employed. Factorial designs will assist in disentangling the relative benefits of the different components of multi-modal interventions.^{151,152}

KQ3. For adults with subjective idiopathic symptoms of tinnitus, what prognostic factors, patient characteristics, and/or symptom characteristics affect final treatment outcomes?

The intent had been to identify from the literature important patient characteristics, symptom characteristics and/or prognostic factors that might affect final treatment outcomes. This systematic review did not identify any literature relevant to addressing this Key Question that met inclusion criteria. Although most studies identified baseline population characteristics, between group analyses of treatment effect were only presented for the main treatment and control groups and not for subgroups differing in the characteristics targeted by KQ3. Furthermore, relationships between patient characteristics and outcomes were not tested (e.g., multivariate regression models evaluating independent contributions of different factors to predict the outcomes of interest). For the included studies, when subgroup results were presented, the focus was not on predicting the effect on prognosis, rather the analysis was more descriptive rather than predictive. This identifies another important gap in the literature. In part this can be related to the evolving issues of diagnosing or establishing the severity of tinnitus, as well as the changing paradigm from the neuroscience perspective.

Applicability

When considering the applicability of study findings in general, the study populations were relatively homogeneous and were limited to mostly middle aged (≥ 50 years of age) persons suffering from predominantly subjective idiopathic tinnitus of mild to moderate severity. Of course, age-related hearing loss also increases markedly with age starting in the fourth decade and hearing loss and tinnitus often co-occur.⁴ Nevertheless, tinnitus is not only a problem for older adults or for people with clinically significant hearing loss. A recent survey estimated tinnitus was prevalent in 12.2 percent of the U.S. population under 44 years of age.^{113,153} However, there is little evidence upon which to draw conclusions about the efficacy of the

therapies in persons younger than 42 years of age. Some studies did focus on industrial workers⁸¹ or veterans,⁹⁷ but these specialized populations may differ from the general population of working-aged people because of the relevance of the link between tinnitus and their occupational exposure to noise and trauma. Importantly, it seems that there may be generational differences in the experience of tinnitus based on recent epidemiological research on adults over the age of 45 years.¹⁵⁴ The finding of generational differences suggests that reports of tinnitus tend to increase with more recent birth cohorts compared with earlier birth cohorts,¹⁵⁴ with participants in a given generation being significantly more likely to report tinnitus than participants from a generation 20 years earlier (OR=1.78; 95% CI, 1.44 to 2.21). Such cohort differences could extend to younger adults, especially given recent concerns about a rise in tinnitus related to exposure to recreational noise.⁶ The generational differences in the reporting of tinnitus may reflect actual changes in prevalence related to lifestyle and environmental differences across cohorts. They may also reflect changes in health attitudes or knowledge that awareness of, and willingness to report, the symptoms. In any case, it is possible that the effectiveness of treatments may differ with age or cohort and it will be important to explore these differences as programs to treat, and possibly even programs to prevent, tinnitus continue to be developed and evaluated.

Tinnitus is a chronic condition and the longest followups in the included studies did not exceed 16 weeks in pharmacological and food supplement studies and 26 weeks in medical interventions. However, followup was extended to 12 months in all of the studies evaluating sound-based treatments^{53,61,92} and even to 18 months for one study.⁹⁸ For the psychological and behavioral interventions, many studies evaluated the effectiveness of treatment immediately post-treatment as well as at one or more later followups. The time intervals ranged from a minimum of 6 weeks¹⁰ to 2 months,⁶² or 3 months^{84,87,102} to 6 months,⁹⁶ but most continued to 1 year^{17,57,95,97,100,104} or even 18 months.¹²⁰ Thus, for the pharmacological and medical intervention categories of intervention, the included studies did not provide data on the medium- to long-term effects of the active treatments. Longer term followup was provided in the studies involving sound-based therapy and psychological/behavioral therapies. These therapies are usually provided by rehabilitative professionals, such as audiologists and psychologists whose practice may put greater emphasis on establishing and maintaining change due to intervention.

Most studies were recruited from clinical or specialty settings. Fewer studies recruited subjects from newspapers and the Internet (open to the public, including associations for tinnitus/hearing loss), which is reflective of the population most likely to benefit from the interventions. However, this method of recruitment might account for the high attrition rates in these studies. Also, for some studies, the subjects represented those who had failed to respond to previous treatments; although the subjects were seen in otolaryngology clinics, they were treated by psychologists, often in conjunction with audiologists. It is not clear what proportion of all tinnitus patients fall into this “failed treatment group”. Two of the studies with failed populations focused on high risk groups. While one of these studies suggests that group educational counseling can be of significant benefit to many tinnitus patients,⁹⁷ the focus on subjects who are veterans may limit the applicability to the general population. This is also an issue for the study that focused only on those 65 years of age and older.⁸⁴

As noted previously, it is difficult to judge the applicability of the doses for the varied interventions in the included studies. The pharmacological and food supplements, sound technologies, and medical interventions would be readily available in primary care, rehabilitation, and audiology settings. Some of the psychological interventions might be more problematic to implement across different healthcare systems.

Many of the studies in this review were conducted in Europe, where the professional model of ‘hearing care/audiology’ is different from that typically seen within the United States. In the United States, the coping/CBT-oriented interventions fall more within the scope of the practice of psychologists, rather than audiologists. If future interventions were to require more of this type of psychological intervention, there would need to be a shift in the training of audiologists or a shift to more team-oriented practice involving both audiologists and psychologists. Added to this, interventions delivered via the Internet are now in use.⁵⁷ Translating all of this into practice has some implications for the education of various health professionals and for the cost/benefit of these newer treatment delivery methods.

Comparative Effectiveness Review Limitations

This CER has several methodological limitations related to the literature search. Although over 9,700 citations were screened, these were limited to ones published in the English language. The studies were restricted to randomized parallel group trials. Crossover trials were reviewed but none had first period data and as such were excluded. Given the diverse interventions, different treatment intervals, and varied followup times, only data across interventions based on the end of treatment and longest followup time was presented. This makes comparison across studies and interventions challenging.

Conflict of interest may be of concern when devices or proprietary interventions are used. A review of the relevant studies revealed that most did not disclose this potential conflict of interest. However, when we were aware of potential conflict of interest, it was noted within the presentation of the results.

There were 22 studies that were eligible for the review but they did not provide measures of variance to allow estimation of an effect size, or provided information in proportions of individuals who changed following treatment and, as such, did not provide baseline measures.

A search of the grey literature was undertaken to identify unpublished trials; however, this avenue did not provide any additional literature. We did not formally assess publication bias as these computations are known to be inaccurate. Based on previous literature that suggests that studies with small sample sizes are at greater risk of publication bias, it was assumed that these groupings of studies were at risk.⁷⁹ Some manufacturers were contacted and scientific industry packages (SIP) for tinnitus-related devices from the MED-EL Corporation (manufacturers of several models of cochlear implants) were received. Although unpublished information was provided regarding research done with their products, none met inclusion criteria. As well, noted by the contacting information officer, MED-EL cochlear implants are not FDA approved in the United States to treat tinnitus. Another information package was received from Neuronetics, manufacturers of the NeuroStar TMS Therapy System[®]. This company has not sponsored any clinical trials, published or unpublished, for their transcranial magnetic stimulation device, nor was this the device used in the TMS studies included in this review; the SIP did not provide any information that had not already been reviewed in the screening process or applied directly to the Key Questions.

A review of trial registries to identify ongoing trials would suggest that research in treatment for tinnitus is a very active area of research (n=26). This review did not identify any studies evaluating sound technologies relative to inactive controls; however, seven trials with such devices are ongoing. Completion of these trials will contribute to future knowledge about the relative importance of these types of interventions.

Summary/Conclusions

Key Question 1

No studies were found addressing the comparative effectiveness of tools used to determine candidacy for treatment. A gap in the literature has been identified.

Key Question 2

Pharmacological and Food Supplement Interventions

We summarized the evidence contained in 16 RCTs that examined pharmacological interventions or food supplements for use in the treatment of tinnitus. The evidence related to six outcomes was examined: TSQoL, subjective loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global QoL. Although some evidence was found to suggest that some therapies led to improvements over primarily placebo comparators on some outcomes, the results were inconsistent and many treatment differences were not statistically significant at $p < 0.05$. The findings of this review agree with the conclusions of previous systematic reviews, which found insufficient, inconsistent, or no evidence of treatment effects.^{7,150,155-158}

In terms of SOE, there is primarily insufficient information to assess whether the published evidence reflects true effects. Effect size estimates were inconsistent or imprecise, and risk of bias was medium. Furthermore, most treatments were evaluated in single studies, which may or may not represent the true effect of any particular therapy. Sample sizes tended to be small (< 100 persons) and power calculations were largely absent from the published reports, leading to the possibility that many studies were underpowered to detect true effects. Lengths of followup were too short to assess the durability of treatment over time and the validity and discriminative ability of many outcome measurement instruments was questionable.

Medical Interventions

Four different medical interventions were evaluated in 11 randomized trials. There was low SOE for rTMS and insufficient evidence for LLLT, ACRN, and acupuncture for improving TSQoL. The studies were generally at high risk of bias, with small sample sizes and were poorly reported. Few studies evaluated subjective loudness, anxiety symptoms, and depression symptoms. There were insufficient studies to evaluate the evidence. No studies evaluating medical interventions assessed the impact on sleep disturbance or global QoL. A clear trend for harms was difficult to specify across the differing interventions. The relative potential for long-term harms was not evaluable in the short term treatment trials included in this grouping.

Sound Technologies Interventions

Four unique RCT, all head-to-head comparisons, evaluated the relative effectiveness of variants of sound-based intervention to determine whether or not benefits, primarily in terms of tinnitus-specific and global QoL and loudness, were enhanced when sound generators were combined with CBT, information, or relaxation or to determine if different versions of sound generators resulted in different outcomes. Half of the studies reported some benefits from treatment, but none demonstrated any significant difference between the treatments that were compared. Similar shortcomings to those discussed for the other interventions also apply to this category of intervention.

Psychological and Behavioral Interventions

Four subcategories of psychological/behavioral interventions were examined: CBT (n=10) and related treatments, TRT-related treatments (n=2), treatments involving primarily relaxation (n=3), and other interventions (n=5), including one involving reading tinnitus books, two emphasizing education, one with yoga, and one with Qigong. Outcomes for TSQoL (19 treatments), subjective loudness (13 treatments), sleep (6 treatments), anxiety (9 treatments), depression symptoms (17 treatments), and global QoL (8 treatments) were measured using a large variety of measures. The SOE for psychological/behavioral interventions was rated as low for the outcome of anxiety symptoms. Low SOE indicates that future research will likely change the magnitude and possibly the direction of the observed effects. Interventions involving CBT were deemed to have low SOE for the outcomes of TSQoL, perceived loudness, anxiety, depression global QoL suggesting that the impact of future research will likely change the magnitude of the effect size to a lesser degree than the other interventions rated as low. Adverse effects were largely not reported in this intervention group. Some studies reported an absence of adverse effects, with the exception of one study where some patients reported that the self-monitoring of the loudness and discomfort caused by their tinnitus resulted in the worsening of those symptoms.

Key Question 3

No studies were found identifying potential prognostic factors. A significant gap in the literature has been identified.

Future Research Recommendations

Previous attempts have been made to identify issues related to the design and conduct of clinical trials evaluating interventions for patients with tinnitus.^{19,159,160} Future research should attempt to incorporate the following recommendations for primary studies evaluating patients with subjective idiopathic tinnitus.

Population

1. Include a broader representation of adult patients with respect to age (range of middle age to old/elderly), gender (equal proportion of men), and ethnicity (increased proportion of non-white or non-Caucasian, or provide broader representation of ethnic groups)
2. Include patients recruited from primary care settings to incorporate a complete spectrum of participants who have tinnitus
3. Capture detailed information about the prior treatments and ensure that future studies do not sample only from subjects who “failed to respond” to previous treatments when receiving new treatments
4. More adequately specify patient medical and mental health histories (i.e., medical comorbidities and previous mental health issues)
5. Collect information on the use of other co-interventions, including psychiatric and complementary and alternative medicine therapies that have the potential to confound and contaminate study interventions

Intervention

1. Establish a clear rationale for the dose used for off-label medications
2. Measure the concomitant use of co-interventions that have the potential to confound interventions (e.g., other pharmacological agents)
3. Specify the training and experience of the person(s) providing the interventions
4. Standards for reporting beam parameters when evaluating LLLT; this will assist in the accurate estimation of the total energy and dose used to administer this treatment.¹⁶¹

Comparator and Study Design

1. Establish sufficient sample sizes to show clinically important differences between treatment groups. Justify the chosen minimum clinically important difference and provide clear justification for the sample size, including a sample size calculation
2. Establish a sufficient sample size to evaluate potentially important confounders such as age, gender, and baseline severity
3. There may be a need to return to Phase II trials to establish therapeutic doses and preliminary efficacy margins. The data from these studies could be used to establish the parameters for Phase III trials
4. Consider open trials to select possible responders and assess their characteristics before undertaking RCT.¹⁹
5. Length of followup should be long enough to study medium- to long-term outcomes given the chronicity of tinnitus)
6. The use of wait list controls need to be carefully considered. Previous analysis suggests over a 6 to 12 week period, subjects can improve from 3 to 8 percent.¹⁶² The population included within studies (age, duration of tinnitus) are important to consider.

Outcomes

1. Aim to encompass three principle components of tinnitus, that include: a) auditory feature of tinnitus perception (intensity, location, masking and pitch), b) emotional features (distress), and c) attentional features (awareness of tinnitus in daily life).¹⁵⁹
2. Identify primary and secondary outcomes within the studies
3. Consider the inclusion of patient-reported outcomes using scales with established psychometric properties, including responsiveness, in the population with subjective idiopathic tinnitus
4. Assess the validity and responsiveness (change over time) of outcome measurement instruments (VAS) in persons with tinnitus prior to using these instruments to evaluate the efficacy of tinnitus interventions
5. Ensure back translation of outcome measurement instruments prior to use in languages other than the language of development.
6. Measure global quality-of-life to capture how persons value the risk-benefit trade-off between the efficacy and adverse effects profiles of treatments under evaluation
7. Conform to the Consolidated Standards of Reporting Trials (CONSORT)¹⁶³ reporting standards for harms. As such, severe and serious events should be defined *a priori* and the use of standardized instruments or terminology for reporting harms should be adopted. Long-term followup may be required to capture harms adequately

Other

1. Develop or improve theoretical models about tinnitus severity and how distress is maintained or exacerbated in these patients.
2. Promote clarity in research and facilitate critical appraisal of the literature, whether for the benefit of a clinician who is seeking practice guidance or a systematic reviewer who is synthesizing evidence, authors of RCT should follow the (CONSORT) Statement. This set of guidelines encourages explicit reporting of RCT features so that readers may understand a study's design, conduct, and analysis
3. Continue to register study protocols in clinical trial registries to allow researchers to evaluate the potential for publication bias and selective outcome reporting. Authors should endeavor to regularly update the information reported within these registries.
4. Studies should be developed to evaluate the natural history and prognostic factors in persons with subjective idiopathic tinnitus

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Appendix A. Search Strategy

Search Strategy: Tinnitus

Medline-OVID

1946-June 13 2012

1. Tinnitus/ or tinnitus.ti.
2. animals/ not humans/
3. 1 not 2
4. limit 3 to english language
5. limit 4 to (case reports or comment or editorial or in vitro or interview or letter or newspaper article or webcasts)
7. 4 not 5

Embase-OVID

1980-June 13 2012

1. Tinnitus/ or tinnitus.ti.
2. limit 1 to english language
3. limit 2 to (book or book series or conference abstract or conference paper or editorial or letter or note)
4. 2 not 3
5. limit 4 to human

Cochrane Controlled Trials Registry-OVID

June 13 2012

1. Tinnitus/ or tinnitus.ti.

PsycINFO-OVID

1967-June 13 2012

1. Tinnitus/ or tinnitus.ti.
2. animals/ not humans/
3. 1 not 2
4. limit 3 to english language
5. limit 4 to (abstract collection or chapter or “column/opinion” or “comment/reply” or dissertation or editorial or encyclopedia entry or letter or obituary or poetry or review-book or review-media or review-software & other)
6. 4 not 5

AMED-OVID

1985-June 13 2012

1. Tinnitus/ or tinnitus.ti.
2. animals/ not humans/
3. 1 not 2
4. limit 3 to english language

Appendix B. Data Extraction Forms

Title & Abstract Screening Form—Level 1

1. **This article was published prior to 1970.**
 - Yes (submit for now)
 - No/unsure
2. **Is this an animal research study? (hint)**
 - Yes (stop)
 - No/Unclear
3. **What is the age group of the research participants? (hint)**
 - Under 18 years (stop)
 - 18 years of age or older/Unclear
4. **Is the research limited to a focus on pulsatile tinnitus only? (hint)**
 - Yes (stop)
 - No/Unclear
5. **Does the research address any of the following:**
 - a) **Tinnitus symptoms [please see (hint) below]**
 - b) **Tinnitus diagnosis; or diagnostic instruments/tests**
 - c) **Tinnitus treatments/interventions (hint)**
 - Yes/Unclear
 - No (stop)
6. **What is the research study design? (hint)**
 - Randomized control trial, clinical control trial, other randomized trial
 - Observational study (cohort, case-control, prospective, retrospective, longitudinal, cross sectional, case series)
 - Systematic review or meta-analysis
 - Narrative or descriptive review or book chapter (stop)
 - Case study (stop)
 - Unclear
7. **Is the publication in English?**
 - Yes/Unclear
 - No

Title & Abstract Level 1 Screening Form Help Sheet

2. Is this an animal research study?
Yes [stop] -- <i>i.e., the research participants are not human, implication of findings are not sufficient to retain citation in our search. If yes, submit this form now.</i>
No/Unclear
3. What is the age group of the research participants?
Under 18 years [stop] <i>-- i.e., a teenage or pediatric population. If yes, submit this form now.</i>
18 years of age or older/Unclear
4. Is the research limited to a focus on pulsatile tinnitus only?
Yes [stop] -- <i>please note: Pulsatile Tinnitus may be referred to as "PT" or "objective tinnitus". Pulsatile tinnitus can be heard by a doctor using a stethoscope (like a pulse), an audible sound emanates from the patient's ears. The sound may have an identified cause.</i> <i>If yes, submit form now.</i>
No/Unclear
5. Does the research address any of the following:
a) Tinnitus symptoms
b) Tinnitus diagnosis; or diagnostic instruments/tests
c) Tinnitus treatments/interventions
Yes/Unclear -- any or all of these subjects themes are considered
<ul style="list-style-type: none"> a) Symptoms – ringing, buzzing in the ears, qualification of the sound perceived (e.g., pitch, volume) b) Diagnosis, diagnostic instruments/tests – i.e., evaluation of the perception of sound, source of sound, and/or impact on patient's daily life (e.g., physical exam, questionnaires, hearing test, CT scan, MRI) c) Treatments/interventions – i.e., medical/surgical (e.g., Pharmacological, Laser, TMJ and Complementary/Alternative Medicine therapies or treatments), technological (e.g., sound maskers, hearing aids, etc.), psychological (e.g., Tinnitus Retraining therapy, Cognitive Behavioral Therapy, etc.); alternative medicine; or combinations thereof
No [stop] -- <i>None of the above are addressed or Tinnitus is a result of another pathology (e.g., a symptom or outcome of another illness/disease/drug, i.e., brain tumor, hypertension, drug side effect/interaction). If so, submit this form now</i>
6. What is the research study design?
RCT or CCT (Randomized control trial, clinical control trial, other research that has been randomized)

<p>Randomized Controlled Trial (RCT): A controlled clinical trial that randomly (by chance) assigns participants to one of two or more groups. There are various methods to randomize study participants to their groups. Identifying words: – randomization; Open trials; Single blind trials; Double blind trials; Triple and quadruple-blind trials; explanatory trial. <i>Example:</i> An example is a <i>randomized controlled trial</i> (RCT) to understand whether calcium tablets work to prevent broken bones in women with low bone density. Women with low bone density are randomly assigned to one of two groups. One group receives calcium and the control group receives a placebo (inactive substance). The number of women who suffer fractures in each group are compared to find out whether calcium works. Controlled Clinical Trial (CCT): A type of clinical trial comparing the effectiveness of one medication or treatment with the effectiveness of another medication or treatment. In many controlled trials, the other treatment is a placebo (inactive substance) and is considered the “control”. <i>Example:</i> An example of a <i>controlled clinical trial</i> is one in which people who took a particular anti-depressive drug were compared with people who did not take the drug to determine its effectiveness in lowering blood pressure.</p>
<p>Observational study (cohort, case-control, case-series)</p> <p>Cohort Study: A clinical research study in which people who presently have a certain condition or receive a particular treatment are followed over time and compared with another group of people who are not affected by the condition. <i>Example:</i> For example, a study that measures effects of tinnitus on quality of life in the same group of men and women with different blood pressure levels over a long period of time.</p> <p>Case-control study (also called a retrospective study): A study that compares two groups of people: those with the disease or condition under study (tinnitus) and a very similar group of people who <i>do not</i> have the disease or condition. Researchers study the medical and lifestyle histories of the people in each group to learn what factors may be associated with the disease or condition. For example, in the case of tinnitus, they may look at environmental noise influences, current drugs being taken, etc.</p> <p>Case Series (also known as a <i>clinical series</i>): a medical research observational study that tracks patients with a known exposure given similar treatment or examines their medical records for exposure and outcome. (Example: 100 patients with tinnitus using a masking device – impact of tinnitus is measured prior to use of device and after; or 100 active-duty soldiers exposed to noise with outcome of tinnitus treated with....). It can be retrospective or prospective and usually involves a smaller number of patients than more powerful case-control studies or randomized controlled trials. Case series may be <i>consecutive</i> or <i>non-consecutive</i>, depending on whether all cases presenting to the reporting authors over a period of time were included, or only a selection. Case series studies do not make comparisons <i>between</i> groups.</p>
<p>Systematic review or meta-analysis</p> <p>Systematic Review: A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis. <i>Example:</i> Scientists collect all the published studies that compare types of treatment for hypertension. They compile the results of these studies, using in-depth statistical methods (a comparative effectiveness review which is a type of <i>systematic review</i>.)</p>
<p>Narrative or descriptive review [stop] Submit form now</p>
<p>Case study [stop] Submit form now</p> <p>Case Study Like a case series, but focused only a single case. WE ARE NOT INTERESTED IN SINGLE CASE STUDIES</p>
<p>Unclear – another type of design is mentioned or the citation does not discuss research design</p>

Title & Abstract Screening Form—Level 2

1. Do any of the following apply to this abstract? If you check any, you are finished and can submit.

- This is not a tinnitus study (stop)
- Publication date is prior to 1970 (stop)
- Language other than English (specify and stop)
- Editorial, comment, conference abstract, letter, opinion piece (stop)
- Animal study (stop)
- Population under 18-years (stop)
- Case study (n=1) (stop)
- Case series (stop)
- Narrative or literature review, dissertations, abstract, or study protocol
- Systematic review
- Meta-analysis (stop)

2. Please consider the following carefully. If you check any, you are finished and can submit this form now.

- Tinnitus symptoms are the side-effect of a drug (ototoxicity)
- The research is focused on another problem/pathology. There are no results related to tinnitus
- The Research focuses on the pathophysiology of tinnitus (see help sheet for examples)
- Tinnitus is the symptom of a vestibular schwannoma or acoustic neuroma; and/or is of a pulsatile nature only

3. The study design includes a comparison/control group (i.e., compares treatment to placebo; treatment to no treatment; a group being treated to a group on a wait list for treatment; one treatment to another treatment, with controls)

- Yes/Unclear (continue)
- No (stop)

Note: The following questions will determine the Key Question(s) this study will be assigned consult review sheet and consider carefully. Check 'yes' to all that apply.

4. This study addresses one or more clinical evaluation measures/tools used to characterize a subjective diagnosis and/or measure the severity of tinnitus. Consult review sheet for examples.

- Yes

5. This study evaluates one or more tinnitus treatments or interventions. Consult review sheet for examples.

- Yes

6. **This study addresses one or more potential predictors of treatment outcomes. This could be characteristics, symptom characteristics, or prognostic factors. Consult review sheet for examples.**
 - Yes
7. **This study is about adults at risk for tinnitus.**
 - Yes [identify at risk group] _____
8. **It is unclear from the abstract if #4, #5, #6, or #7 apply.**
 - Yes
 - No abstract available

Title & Abstract Level 2 Screening Form Help Sheet

Question 2: Response 3: Pathophysiology of tinnitus i.e., brain or neuron activity patterns, brain-based mechanisms, activity in the brain or specific regions in the brain; brain responses, function, process (mechanisms in the central nervous system), plasticity, neuronal firing, varied otoacoustic emissions [OAE], etc. The research does not investigate ways of measuring the subject's perception of tinnitus or treatments for tinnitus

Question 4: Clinical evaluation measures

Scales/questionnaires used to assess severity of tinnitus: Tinnitus Handicap Inventory, Tinnitus Reaction Questionnaire, Tinnitus Functional Index, Visual Analog Scale, and Tinnitus Severity Index, etc.

Question 5: Tinnitus Interventions: Any treatment/therapy (or combination of treatments/therapies) used to reduce or help cope with tinnitus including **but not limited to:**

Medical/ Surgical	<ul style="list-style-type: none"> ■ Pharmacological treatments <ul style="list-style-type: none"> □ Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, and trimipramine) □ Selective serotonin-reuptake inhibitors: fluoxetine and paroxetine □ Other: trazodone; anxiolytics (e.g., alprazolam); vasodilators and vasoactive substances (e.g., prostaglandin E1); intravenous lidocaine; gabapentin; Botox (botulinum toxin type A); and pramipexole) ■ Laser treatments ■ TMJ treatment: dental orthotics and self-care; surgery ■ Transcranial Magnetic Stimulation ■ Complementary and alternative medicine therapies: <i>G. biloba</i> extracts; acupuncture; hyperbaric oxygen therapy; diet, lifestyle and sleep modifications (caffeine avoidance, exercise)
Sound Treatments	Hearing Aids; Sound generators / maskers (both wearable and stationary); Cochlear implants; Neuromonics; Tinnitus Retraining Therapy
Psychological / Behavioral	Cognitive behavioral therapy; Biofeedback; Education; Relaxation therapies; Progressive Tinnitus Management

Question 6: Predictors of treatment outcomes

Prognostic Factors:	Length of time to treatment after onset, audiological factors (degree and type of hearing loss, hyperacusis, loudness tolerance, masking criteria, etc.), head injury, anxiety, mental health disorders, duration of tinnitus
Patient Characteristics	Age, gender, race, medical or mental health comorbidities, socioeconomic factors, noise exposure (environmental, recreational and work-related, including active military duty personnel or veterans, and occupational hazards), involvement in litigation, third party coverage (health insurance)
Symptom Characteristics	Origin/presumed etiology of tinnitus, tinnitus duration since onset, subcategory of tinnitus, severity of tinnitus

Full Text Screen

- 1. Do any of the following apply to this paper? If yes, check and submit this form now.**
 - It is not English
 - It does not involve humans
 - Subjects are under 18 years of age
 - The tinnitus being studied is pulsatile
 - Tinnitus is the side-effect of a drug (ototoxicity)
 - This is a case study/report (n=1)
 - This is a case series (specify number of subjects and stop) _____
 - Article unavailable to order
- 2. Is this study ONLY to determine the prevalence of tinnitus in a population group at any given time?**
 - Yes (stop)
 - No (continue)
- 3. Is this study ONLY to determine various effects of tinnitus on an individual (e.g., effect on memory, etc)?**
 - Yes (stop)
 - No (continue)
- 4. Is this study ONLY focused on ways of determining whether a patient has ‘malingered’ tinnitus?**
 - Yes (stop)
 - No (continue)
- 5. Tinnitus is the result of issues in the middle ear (i.e., mechanics, otitis media, otosclerosis, eustachion tube, pressure, etc.) or the intervention is a stapedectomy or tympanoplasty.**
 - Yes (stop)
 - No (continue)
- 6. Is this a primary study (i.e., the original publication of new data and results)?**
 - Yes, e.g. RCT, cohort study, etc. (continue)

- No, it is a systematic review or meta-analysis (stop)
- No, it is not primary research (e.g., editorial, comment, conference abstract, letter, opinion piece, protocol, narrative/DESCRIPTIVE study)[Stop]

7. Does the study COMPARE:

- More than one tool/method that RESULT in candidacy for further evaluation or treatment?
- Group treatment outcomes (e.g. treatment to placebo; treatment to no treatment; one treatment to another treatment, with controls)
- Both a and b
- None of the above (comparators do not meet inclusion criteria)
- Insufficient detail for aggregation of data/results

Full Text Screening Form Help Sheet

1. Do any of the following apply to this paper? IF YOU CHECK ANY ANSWERS BELOW YOU ARE FINISHED THIS REVIEW.
 - a. It is not in English (stop)
 - b. It does not involve humans (stop)
 - c. Subjects are under 18 years of age (stop)
 - d. The tinnitus being studied is of a pulsatile nature. NOTE: Pulsatile Tinnitus may be referred to as PT, Objective, OT, or Functional. Pulsatile tinnitus can be heard by a doctor using a stethoscope (like a pulse), an audible sound emanates from the patient's ears. The sound HAS AN IDENTIFIABLE CAUSE (ACOUSTIC NEUROMA, for example). Our interest is in subjective (only the patient can hear it), idiopathic (of unknown origin/cause) tinnitus
 - e. Tinnitus is the side-effect of a drug (ototoxicity). NOTE: if the article is about a drug and mentions tinnitus as a symptom of taking the drug, we are not interested. IN GENERAL, IF A CHANGE IN MEDICATION WOULD LEAD TO TINNITUS DISAPPEARING, the study should be excluded here.
 - f. This is a Case report/study (N=1) Note: a case report is a descriptive study of a single individual in which the possibility of an association between an observed effect and a specific exposure is based on a detailed clinical evaluation and history of the individual.
 - g. This is a case series. [Specify number of subjects and stop] Note: A case series is a descriptive study that follows a group of patients who all have the same diagnosis or who are all undergoing the same procedure/treatment over a certain period of time. Case series do not employ control groups. Results of case series can generate hypotheses that are useful in designing further studies, including randomized controlled trials. However, no causal inferences should be made from case series regarding the efficacy of the investigated treatment.
2. Is this study only to determine the prevalence of tinnitus in a population group at any given time? NOTE: A prevalence study could be in a general or a specialized population. The study may look at how many people in Timbuktu have tinnitus or what percentage of the elderly people in Timbuktu over 60 has tinnitus. If this is only a prevalence study we are not interested. HOWEVER, if the study on the elderly with tinnitus in Timbuktu then went on to

do further evaluation/treatment research with that population, you would not exclude the study at this point.

3. Is this study only to determine various effects of tinnitus on an individual (e.g., effect on sleep or brain wave patterns; effect on memory)? Yes [STOP] NOTE: We are not interested in research on how people with tinnitus have memory problems or what the brain wave patterns of people with tinnitus are, or the fact that people with tinnitus can't sleep. If the study only looks at a way that tinnitus affects an individual but does not look at ways of determining their candidacy for treatment or is not an evaluation of a treatment outcome, it should be excluded.
4. Is this study only focused on ways of determining whether a patient has 'malingering' tinnitus? Fabricating or exaggerating the symptoms of tinnitus for a variety of "secondary gain" motives; for example to claim insurance benefits, avoid work, etc.
5. Does this report describe a primary study (i.e., the original publication of new data and results)
6. Does the study design compare:
 - a. More than one method of evaluation to determine candidacy for treatment i.e., the study compares two different scales/questionnaires (tinnitus handicap inventory vs. functional tinnitus index) used to assess severity of tinnitus in order to determine need for further treatment.
 - b. Group treatment outcomes (i.e., one group gets a treatment drug compared to one getting a placebo; one group gets treatment compared to another group getting no treatment; a group being treated compared to a group on a waiting list for treatment; one treatment compared to another treatment; a before/after treatment comparison; within-group comparison; between-group comparison).
 - c. Both a and b
 - d. There is no comparison of methods for evaluating tinnitus or tinnitus treatment outcomes in this study

Data Extraction

1. Study design:

- Randomized clinical trial
- Nonrandomized trial (quasi-experimental, interrupted time series design, etc.)
- Controlled clinical trial (not randomized)
- Cohort, prospective
- Cohort, retrospective
- Case-control
- Cross-sectional
- Before-after
- Other (identify) _____

2. Is there any reason this study should be excluded?

- Yes (identify) _____
- No (continue)

3. Is this a pilot study?

- Yes
- No

4. Country

5. Setting (e.g., primary care, ENT, audiology, neurology, mental health service, community, internet, other-identify, etc.)

6. Is this the primary diagnosis of subjects in this study subjective (idiopathic, nonpulsatile) tinnitus?

- Yes
- No, tinnitus is secondary to (a symptom of) another diagnosis [identify primary diagnosis-for example Meniere's disease]_____

7. If tinnitus is secondary to another diagnosis, are there results provided specific to the effect of an intervention on the tinnitus symptoms?

- Not applicable
- Yes (continue)
- No (submit form now)

8. Please describe the population included in the study (selection criteria and the number excluded if provided):

9. Number of intervention groups _____

10. Number of control groups _____

11. Please report the AGE CHARACTERISTICS (if applicable):

Characteristics	All Patient n=? _____	Intervention Group 1 (I1) n=? _____	Control Group 1 (C1) n=? _____	Identify Group (I# or C#) and n=? _____	Identify Group (I# or C#) and n=? _____	Identify Group (I# or C#) and n=? _____	Identify Group (I# or C#) and n=? _____
Mean							
Standard Dev.							
Standard Error							
Median							
Inter Quartile Range							
Min							
Max							

12. NOTES for AGE

13. Please report GENDER (if applicable):

Gender	n/% All Patient _____	n/% Intervention 1 (I1) _____	n/% Control 1 (C1) _____	n/% Identify Group (I# or C#) _____	n/% Identify Group (I# or C#) _____
FEMALE					
MALE					

14. a) NOTES for GENDER

15. Please report RACE/ETHNICITY (if applicable):

Characteristics	n/% All Patient	n/% Intervention 1 (I1)	n/% Control 1 (C1)	n/% Identify Group (I# or C#)	n/% Identify Group (I# or C#)	n/% Identify Group (I# or C#)	n/% Identify Group (I# or C#)
White/Caucasian							
African-American/Black							
Hispanic							
Aboriginal							
Asian							
Other 1							
Other 2							
Other 3							

If other 1, please specify race/ethnicity: _____

If other 2, please specify race/ethnicity: _____

If other 3, please specify race/ethnicity: _____

16. Identify any medical and/or mental health comorbidities. Record any data and source location if applicable.

17. Identify the treatment intervention in this study. (Note: if the study is comparing the effectiveness of two or more interventions, identify all. Use text box to add brief detail- i.e., drug name(s), device name(s), etc.)

- Pharmacological [identify drug(s) being studied] _____
- Laser _____
- Temporal Mandibular Joint-TMJ (dental orthotics, self-care, surgery) _____
- TMS (transcranial magnetic stimulation) _____
- Ginko Biloba extracts _____
- Acupuncture _____
- Hyperbaric oxygen therapy _____
- Electrical Stimulation _____
- Diet modification(s) [identify] _____
- Sleep therapy/modification _____
- Lifestyle changes (not diet or sleep) [identify] _____
- Hearing aids _____
- Cochlear implants _____
- Sound generators/maskers (wearable) [identify make if provided] _____
- Sound generators/maskers (stationary) [identify make if provided] _____
- Neuromonics _____
- Tinnitus Retraining Therapy (TRT) _____
- Cognitive Behavioral Therapy (CBT) _____
- Patient Education _____
- Relaxation therapies _____
- Progressive Tinnitus Management (PTM) _____
- This study is evaluating a combination of tinnitus interventions [identify the combination] _____
- Other [identify] _____
- Other [identify] _____
- Other[identify] _____
- Other[identify] _____
- Other[identify] _____
- This study ONLY focuses on tools/measures that RESULT in candidacy for treatment.

18. Interventions: *Please describe intervention(s) with sufficient detail for replication. Include duration of treatment, intensity of treatment, if feasible. (Length of study; number of follow-ups). Include page number sources of information.

19. If the study only discusses one treatment intervention, what is the Intervention compared to?

- Usual care
- No treatment
- Placebo
- Wait list
- Not-applicable
- Other (identify) _____

20. Number of participants allocated to Intervention Group 1 at baseline _____

21. Number of participants in Intervention Group 1 at final follow-up _____

22. Number of participants allocated to Intervention Group 2 at baseline _____

23. Number of participants in Intervention Group 2 at final follow-up _____

24. Number of participants allocated to the control group (if not a within-subject study). _____

25. Number of participants in control group at final follow-up _____

26. Reasons for withdrawal? (Identify group, # of withdrawals, and any reasons provided-with # per reason if included)

27. Identify source of funding (NR if not reported)

Additional Notes

Modified Jadad

1. Is this a RCT study?

- Yes (continue)
- No it is a cross section (stop and use cross-sectional form) _____
- No it is a cohort (stop and use NOS cohort form)
- Not it is a case control (stop and use case control form)
- Other (identify and stop) _____

2. Reported as randomized

- Yes (1 Point)
- No

3. Randomization is appropriate

- Yes (1 Point)
- No (-1 Point)
- Not Described

4. Double blinding is reported

- Yes (1 Point)
- No

5. Double blinding is appropriate

- Yes (1 Point)
- No (-1 Point)
- Not Described

6. Withdrawals are reported by number and reason per arm

- Yes (1 Point)
- No

7. Jadad Score (/5)

- 0
- 1
- 2
- 3
- 4
- 5

8. Method(s) used to assess adverse events is described

- Yes(1 Point)
- No

9. Method(s) of statistical analysis is described

- Yes (1 Point)
- No

10. Inclusion and/or exclusion of the requirements is reported

- Yes (1 point if at least one of the requirements is reported)
- No

11. Modified Jadad score (/8)

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8

12. Was the allocation adequately concealed? (e.g., pharmacy controlled randomized scheme, sequentially numbered opaque, sealed envelope, sequentially numbered/coded identical containers, central randomization by phone)

- Yes
- No
- Unclear

13. Was the analysis based on intention to treat principle?

- Yes
- No
- Unclear

14. Was the sample size justified?

- Yes
- No
- Unclear

TNT Outcomes Continuous

1. Identify the outcomes of interest in this study (check all that apply):

- Sleep
- Discomfort/distress
- Depression
- Self-reported loudness
- Quality of life
- Time to improvement
- Severity
- Worsening of tinnitus
- Sedation
- Surgical complications
- Other (identify) _____
- Other (identify) _____
- Other (identify) _____
- Other (identify) _____
- Other (identify) _____
- Other (identify) _____
- Other (identify) _____

2. Specify the outcome measure(s) for each outcome you identified above (use acronyms where provided)

- Sleep _____
- Discomfort/distress _____
- Anxiety _____
- Depression _____
- Self-reported loudness _____
- Quality of life _____
- Tinnitus severity _____
- Time to improvement _____
- Worsening of tinnitus _____
- Sedation _____
- Surgical Complication _____
- Other _____
- Other _____
- Other _____
- Other _____
- Other _____
- Other _____
- Other _____

3. Further definition of outcomes identified above (e.g., units of measurement, full name of tools/measures –Beck Depression Inventory, validated instruments –ref#?). Provide page/paragraph numbers. (i.e., p.12,para3)

4. Please identify data type (if continuous AND dichotomous, check both). Use table for continuous and text box below table for dichotomous):

- Continuous
- Dichotomous

**5. Outline from where you took the data (i.e., variables Sleep and Distress from Table 2, or page and paragraph number).
USE THIS BOX TO REPORT DICHOTOMOUS DATA if applicable.**

6. If there is relevant PRE-POST data for the above outcomes that does not fit within the table above, please add here.

7. Add all Intention-to-treat analysis information here.

8. Very briefly summarize the main conclusion(s) of this article.

9. Are there any sub-group analyses provided in the paper? (See example sheet for breakdowns/examples. Only identify groups for which PRE/POST intervention data is provided).

- Analysis of the effect of patient characteristics on treatment outcomes _____
- Analysis of the effect of symptoms characteristics on treatment outcomes _____
- Analysis of the effect of prognostic factors on treatment outcomes _____
- None of the above

10. Study design to determine Quality Analysis form:

- RCT, CCT
- Non randomized trial
- Cohort (prospective; retrospective; before-after; time-series)
- Case control
- Cross section
- Other observational

Appendix C. Excluded Studies

Aazh H, Moore BCJ, Glasberg BR. Simplified form of tinnitus retraining therapy in adults: A retrospective study. *BMC Ear Nose Throat Disord.* 2008;8(1):7.

Exclude: Non-randomized head-to-head

Abelson TI. Long-term bilateral tinnitus. *JAMA.* 1985;253(19):2830. PMID:3989951.

Exclude: Not a primary study

Acrani IO, Pereira LD. Temporal resolution and selective attention of individuals with tinnitus. *Profono.* 2010;22(3):233-8. PMID:21103711.

Exclude: Only determined various effects

Adlington P, Warrick J. Stellate ganglion block in the management of tinnitus. *-J Laryngol Otol.* 1971;85(2):159-68. PMID:4396190.

Exclude: Case study or series

Ahmad R, Raichura N, Kilbane V, et al. Vancomycin: A reappraisal. *BMJ Clin Res Ed.* 1982;284(6333):1953-4. PMID:6805786.

Exclude: Not a primary study

Ahmad S. Venlafaxine and severe tinnitus. *Am Fam Physician.* 1995;51(8):1830. PMID:7762476.

Exclude: Not a primary study

Albrecht III CR, Gambert SR. Botanical and diet-based biological therapies and their use by older persons: Part I. *Clin Geriatr.* 2005;13(1):26-34.

Exclude: Not a primary study

Aleksic M, Schutz G, Gerth S, et al. Surgical approach to kinking and coiling of the internal carotid artery. *J Cardiovasc Surg.* 2004;45(1):43-8. PMID:15041936.

Exclude: Tinnitus is somatic

Al-Jassim AH. The use of Walkman Mini-stereo system as a tinnitus masker. *J Laryngol Otol.* 1988;102(1):27-8. PMID:3343558.

Exclude: Non-randomized head-to-head

Almeida TA, Samelli AG, Mecca FN, et al. Tinnitus sensation pre and post nutritional intervention in metabolic disorders. *Profono.* 2009;21(4):291-7. PMID:20098946.

Exclude: Insufficient detail of outcome data/not extractable

Andersson G, Airikka M-L, Buhrman M, et al. Dimensions of perfectionism and tinnitus distress. *Psychol Health Med.* 2005;10(1):78-87.

Exclude: Only determined various effects

Andersson G, Edsjo L, Kaldo V, et al. Tinnitus and short-term serial recall in stable versus intermittent masking conditions. *Scand J Psychol.* 2009;50(5):517-22. PMID:19778399.

Exclude: Only determined various effects

Andersson G, Ingerholt C, Jansson M. Autobiographical memory in patients with tinnitus. *Psychol Health.* 2003;18(5):667-75.

Exclude: Only determined various effects

Andersson G, Juris L, Classon E, et al. Consequences of suppressing thoughts about tinnitus and the effects of cognitive distraction on brain activity in tinnitus patients. *Audiol Neuro Otol*. 2006;11(5):301-9. PMID:16837798.

Exclude: Only determined various effects

Andersson G, Kaldo V, Stromgren T, et al. Are coping strategies really useful for the tinnitus patient? An investigation conducted via the internet. *Audiol Med*. 2004;2(1):54-9.

Exclude: Only about prevalence

Andersson G, Keshishi A, Baguley DM. Benefit from hearing aids in users with and without tinnitus. *Audiol Med*. 2011;9(2):73-8.

Exclude: Non-randomized head-to-head

Andersson G, Kyrre SO, Kaldo V, et al. Future thinking in tinnitus patients. *J Psychosom Res*. 2007;63(2):191-4. PMID:17662756.

Exclude: Only determined various effects

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Exclude: Only about prevalence

Appendix D. Publications Not Eligible for Extraction

Table D1. Pharmacological or food supplement interventions and outcomes: Honorable mention group (n=10)

Pharm/Food Intervention	#	Specific Intervention	Tinnitus-Specific QoL	Loudness	Sleep	Anxiety Symptoms	Depression Symptoms	Global QoL	Adverse Effects
Anti-depressant drugs		INACTIVE COMPARATOR							
	1	Amitriptyline vs. Placebo Bayar, 2001 ¹	ATA-Q						
	2	Nortriptyline vs. Placebo Dobie, 1993 ²	IOWA, Tinnitus interference (self-report),	Self-reported	HDS sub-scale	HAS, Sheehan's Disability Scale	BDI, HDS		
Psychoactive (Neurotransmitter) drugs		INACTIVE COMPARATOR							
	1	Gabapentin (GABA analogue – GABAergic) vs. placebo Dehkordi, 2011 ³	TSI	subjective					
Other drugs		INACTIVE COMPARATOR							
	1	Melatonin and Sulodexide vs. control group Neri, 2009 ^{4,5}	THI						
	2	Melatonin alone vs. control group Neri, 2009 ^{4,5}	THI						
	3	Memantine vs. Placebo Figueiredo, 2008 ⁶	THI						
	4	Atorvastatin vs. Placebo Olzowy, 2007 ⁷	Tinnitus Score						
	5	Misoprostol vs. Placebo Akkuzu, 2004 ⁸	Self-reported	Self-reported	Self-reported				
	6	Cinnarizine vs. Placebo Podoshin, 1991 ⁹	Self-reported						
	7	Neramexane vs. Placebo Suckfüll, 2011 ¹⁰	THI, TA (annoyance)	Likert-scale				Likert-scale	
	8	AM-101 injection vs. Placebo Muehlmeier, 2011 ¹¹	THI	subjective					

Table D1. Pharmacological or food supplement interventions and outcomes: Honorable mention group (n=10) (continued)

Pharm/Food Intervention	#	Specific Intervention	Tinnitus-Specific QoL	Loudness	Sleep	Anxiety Symptoms	Depression Symptoms	Global QoL	Adverse Effects
<i>Other drugs (cont'd)</i>		HEAD TO HEAD							
	1	Melatonin and Sulodexide vs. Melatonin alone Neri, 2009 ^{4,5}	THI						
	2	Cinnarizine vs. Biofeedback Podoshin, 1991 ⁹	Self-reported						
	3	Cinnarizine vs. Acupuncture Podoshin, 1991 ⁹	Self-reported						

Abbreviations: GABAB1 = gamma-aminobutyric acid B1; gen = generation; med/surg = medical/surgical; PDE5 = phosphodiesterase type 5; QoL = quality of life; rTMS = repetitive transcranial magnetic stimulation; SARI = serotonin antagonist reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; vs. = versus

Table D2. Medical interventions and outcomes: Honorable mention group (n=4)

Medical Intervention	#	Specific Intervention	Tinnitus-Specific QoL	Loudness	Sleep	Anxiety Symptoms	Depression Symptoms	Global QoL	Adverse Events
RTMS		INACTIVE COMPARATOR							
	1	1Hz rTMS vs. sham Khedr, 2007 ¹²	THI, self-reported						
	2	10Hz rTMS vs. sham Khedr, 2007 ¹²	THI, self-reported						
	3	25Hz rTMS vs. sham Khedr, 2007 ¹²	THI, self-reported						
	4	Electromagnetic stimulation vs. Placebo Roland, 1993 ¹³	Self-reported						
		HEAD TO HEAD							
	1	1Hz rTMS vs. 10Hz rTMS Khedr, 2007 ¹²	THI, self-reported						
	2	1Hz rTMS vs. 25Hz rTMS Khedr, 2007 ¹²	THI, self-reported						
	3	10Hz rTMS vs. 25Hz rTMS Khedr, 2007 ¹²	THI, self-reported						
	Neuromodulation		HEAD TO HEAD						
1		InterX (electrical neuro stimulation) vs. Osteopathic manipulations Bonaconsa, 2010 ¹⁴	THI, VAS						
Laser		INACTIVE COMPARATOR							
	1	Laser therapy vs. Placebo Gungor, 2008 ¹⁵	Self-reported	Self-reported					

Table D3. Sound treatments/technologies interventions and outcomes: Honorable mention group (n=4)

Sound Treatment/ Technology	#	Specific Intervention	Tinnitus-Specific QoL	Loudness	Sleep	Anxiety Symptoms	Depression Symptoms	Global QoL	Adverse Events
		INACTIVE COMPARATOR							
	1	HLSAME ADT vs. WLG Herraiz, 2010, ¹⁶	THI	VAS					
	2	HLNONSAME ADT vs. WLG Herraiz, 2010, ¹⁶	THI	VAS					
	3	Aural masker vs. placebo masker Jakes, 1992, ¹⁷	TEQ, IWDA, CCEI		TEQ- sub scale				
	4	Group cognitive therapy + aural masker vs. placebo masker Jakes, 1992, ¹⁷	TEQ, IWDA, CCEI		TEQ- sub scale				
		HEAD TO HEAD							
	1	HLSAME ADT vs. HLNONSAME ADT Herraiz, 2010, ¹⁶	THI	VAS					
	2	Hearing aid plus counselling vs. counselling only Searchfield, 2010, ¹⁸	THQ						
	3	Tinnitus Masking vs. pharmacotherapy Pandey, 2010, ¹⁹	THI			HAS	HAD		
	4	Tinnitus Masking vs. yoga (Bhramari Pranayama) Pandey, 2010, ¹⁹	THI			HAS	HAD		
	5	Tinnitus Masking vs. combination therapy Pandey, 2010, ¹⁹	THI			HAS	HAD		
	6	Aural masker vs. Group cognitive therapy + aural masker Jakes, 1992, ¹⁷	TEQ, IWDA, CCEI		TEQ- sub scale				

Table D4. Psychological/behavioral interventions and outcome measures: Honorable mention group (n=6)

Psych/Beh Intervention	#	Specific Intervention	Tinnitus-Specific QoL	Loudness	Sleep	Anxiety Symptoms	Depression Symptoms	Global QoL	Adverse Events
CBT / CBT combination	INACTIVE COMPARISONS								
	1	Group cognitive therapy vs. WLC Jakes, 1992, ¹⁷	TEQ, IWDA, CCEI		TEQ- sub scale				
	2	Group cognitive therapy + aural masker vs. WLC Jakes, 1992, ¹⁷	TEQ, IWDA, CCEI		TEQ- sub scale				
	HEAD TO HEAD COMPARISONS								
		Group cognitive therapy vs. Group cognitive therapy + aural masker Jakes, 1992, ¹⁷	TEQ, IWDA, CCEI		TEQ- sub scale				
Relaxation	INACTIVE COMPARATOR								
	1	Relaxation & exposure vs. WLC Lindberg, 1989, ²⁰	Tinnitus control (VAS), discomfort (VAS)	VAS					
	2	Relaxation & distraction vs. WLC Lindberg, 1989, ²⁰	Tinnitus control (VAS), discomfort (VAS)	VAS					
	HEAD to HEAD								
	1	Relaxation & distraction vs. Relaxation & exposure Lindberg, 1989, ²⁰	Tinnitus control (VAS), discomfort (VAS)	VAS					
Other psych/ beh	INACTIVE COMPARATOR								
	1	Biofeedback vs. Control Podoshin, 1991, ⁹	Self-reported						

Table D4. Psychological/behavioral interventions and outcome measures: Honorable mention group (n=6) (continued)

Psych/Beh Intervention	#	Specific Intervention	Tinnitus-Specific QoL	Loudness	Sleep	Anxiety Symptoms	Depression Symptoms	Global QoL	Adverse Events
<i>Other psych/ beh (cont'd)</i>		HEAD TO HEAD							
	1	yoga (Bhramari Pranayama) vs. pharmacotherapy Pandey, 2010, ¹⁹	THI			HAS	HAD		
	2	yoga (Bhramari Pranayama) vs. combination therapy Pandey, 2010, ¹⁹	THI			HAS	HAD		
	3	Client centered hypnotherapy vs. counseling Mason, 1996, ²¹	TSSS						
4	Biofeedback vs. Stomatognathic treatment Erlandsson, 1991, ²²	Self-reported							

Abbreviations: ACT = acceptance and commitment therapy; CBT = cognitive behavioral training; psych/beh = psychological/behavioral; EMG = electromyography; TCT tinnitus coping therapy; TRT = tinnitus retraining therapy; vs. = versus; WLC = wait list control

Appendix D. References

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Appendix E. Characteristics of Included Studies Evidence Tables

Table E1. Pharmacological or food supplement interventions and outcomes (n=16)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Aoki, ⁷⁶ 2012 Japan	<p>Baseline sample: Total n = 60; Interven: n = 30; Cntrl: n = 30 Setting: Department of Otolaryngology Mean age (SD): Interven: 64.9y (11.3); Cntrl: 61.6y (11.1) Gender: 20.7% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: > 6 months Severity of tinnitus: unilateral chronic Number of dropouts: 2 Reasons for dropouts: Adverse events Audiological factors: 4-tone average better ear (dB) Interven: 31.8 +/-18.5; Cntrl 31.3 +/-20.4. Four-tone average worse ear (dB): Interven: 60.7+/-23.6; Cntrl: 56.8+/-22.8 Comorbidities: NR</p>	<p>Lyophilized powder of enzymolyzed honeybee larvae (720 mg/4 capsules/day)</p> <p>Comparator: Placebo (hydrogenated dextrin; 720 mg/4 capsules/day) indistinguishable in appearance or odor</p> <p>Duration of treatment: 12 weeks Number of follow ups: 3 (4, 8 and 12 weeks) Duration of study: November 2009 to October 2010</p>	<p>Depression (THI-sub)</p> <p>TS-QOL (THI*, VAS)</p>	<p>The lyophilized powder of enzymolyzed honeybee larvae was not superior to placebo with regard to the total score on the Tinnitus Handicap Inventory and the visual analog scale.</p> <p>Adverse Events: “experienced discomfort after taking the capsules” (1 Interven; 1 Cntrl)</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Arda, ⁷⁷ 2003 Turkey	<p>Baseline sample: Total n = 50; Interven n = 30; Cntrl n = 20 Setting: ENT Clinic Mean age (SD): Total range: 21-74 y; Interven: 55 y (14.3); Cntrl: 51.2 y (12.8) Gender: Interven: 42.8% male; Cntrl: 30.7% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: Interven: 39.39 months (\pm34.30); Cntrl: 26.08 months (\pm21.32) Severity of tinnitus: unilateral chronic Number of dropouts: 9 Interven n = 2; Cntrl n = 7 Reasons for dropouts: Non-compliance Interven n = 2; Cntrl n = 7 Audiological factors: Continuous tinnitus Interven 10 (35.7%); Cntrl 6 (46.2%) Comorbidities: Not reported</p>	<p>Zinc Interven: 28 patients in the zinc group were given 50 mg zinc per day for 2 months (Zinco 220, 50 mg).</p> <p>Comparator: Placebo – 1 starch tablet daily for 2 months</p> <p>Duration of treatment: 2 months Number of follow-ups: 1 Duration of study: April 2000 to May 2001</p>	Loudness (Subjective score 0-7)	<p>Clinically favorable progress was detected in 46.4% of patients given zinc. The severity of subjective tinnitus decreased in 82% of the patients receiving zinc (NS). The mean of subjective tinnitus decreased from 5.25 \pm 1.08 to 2.82 \pm 1.81 ($P < 0.001$).</p> <p>Adverse Events: 2 patients in the zinc group had minor gastric disturbances</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Azevedo, ⁷² 2005 Brazil	<p>Baseline sample: Total n = 50 Interven n = 25; Cntrl n = 25 Setting: Otorhinology Hospital clinic Mean age (SD): 60 y; range 35y to 82y Gender: 58% male</p> <p>Presumed etiology of tinnitus: sensorineural Duration of tinnitus: 9.8% <1y; 53.7% 1 to 7y; 36.6% >7y Severity of tinnitus: NR Number of dropouts: Interven n = 2; Cntrl n = 7 Reasons for dropouts: Side effects: Interven (1); Cntrl (5) Family pressures: Interven (1); Cntrl (2) Audiological factors: conductive and mixed hearing loss were excluded Comorbidities: Hearing loss (59.4%); Dizziness (46.9%); Hyperacusis (9.3%)</p>	<p>Double Blind RCT Acamprosate 333mg, TID</p> <p>Comparator: Placebo, TID</p> <p>Duration of treatment: 90 days Number of followups: 3 at 30 days, 60 days, 90 days Duration of study: October 2003 to October 2004</p>	<p>TS-QOL (subjective)</p>	<p>A high index of success in the relief of tinnitus, about 86.9%.n 47.8% of the cases, more than 50% relief was found.</p> <p>Authors conclude that Acamprosate, a drug used in the treatment of alcoholism, is a safe and successful alternative for sensorineural tinnitus' treatment.</p> <p>Adverse events: The incidence of side effects was low, 12%, all of them mild (epigastralgia, choking).</p>
Dib, ⁸¹ 2007 Brazil	<p>Baseline sample: Total n = 85 Interven n = 43; Cntrl n = 42 Setting: NR Age Range: 45 to 80 y Gender: Interven: 41.9% male; Cntrl: 26.2% male</p> <p>Presumed etiology of tinnitus: no defined etiology disease in the middle ear Duration of tinnitus: 1 yr Severity of tinnitus: NR Number of dropouts: 0 Reasons for dropouts: N/A Audiological factors: Normal audiograms, mild/moderate sensorineural hearing loss Comorbidities: NR</p>	<p>Trazodone (antidepressant) 50mg per tablet, single night dose for 60 continuous days. If important side effects were seen, the medication was discontinued.</p> <p>Comparator: Placebo</p> <p>Only the pharmacist knew what drug was being given to which patient.</p> <p>Duration of treatment: 60 days Number of follow ups: 1 Duration of study: February to June (2005)</p>	<p>G-QOL (VAS)</p> <p>TS-QOL (VAS-s*; VAS-d)</p>	<p>There was a significant improvement in intensity, discomfort and life quality in both groups after treatment; however, there was no significant difference between the drug and placebo groups.</p> <p>Trazodone was not efficient in Cntrlling tinnitus in the patients evaluated under the doses utilized.</p> <p>Adverse Events: No AEs in 83.7% of the Treatment group. AEs included: apathy, hypertensive crisis, epigastralgia, nausea, sleepiness</p> <p>Sleepiness Interven = 3 (7%); Cntrl = 1 (2.4%)</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Drew, ⁸⁴ 2001 United Kingdom	Baseline sample: Total n = 1,121 Interven n = 559; Cntrl n = 562 Setting: mail and telephone Mean age (SD): Int: 52.9y (9.3); Cntrl: 53.0y (9.3) Gender: Int 69% male; Cntrl 69% male Presumed etiology of tinnitus: NR Duration of tinnitus: >12 months; ≤5 y Int: 10.0y (8.3); Cntrl: 10.1y (8.3) Severity of tinnitus: NR Number of dropouts: Interven: 99 (17.7%); Cntrl: 87 (15.5%) Reasons for dropouts: didn't return questionnaires Audiological factors: NR Comorbidities: NR	Ginkgo Biloba: 252 tablets containing 50 mg standardized extract LI 1370 (containing 25% flavonoids, 3% ginkgolides, and 5% bilobalides) – instructed to take 3 tablets daily Comparator: Placebo tablets identical to the active tables in shape, size, color and packaging. Duration of treatment: 12 weeks Number of followups: 3 (4, 12, 14 weeks) Duration of study: NR	TS-QOL (TSQ- 21) Loudness (VAS)	50 mg <i>Ginkgo biloba</i> extract LI 1370 given 3 times daily for 12 weeks is no more effective than placebo in treating tinnitus. Adverse events: The incidence of AEs was similar between the treatment groups. AEs included: gastrointestinal upset, dizziness, headache, mouth ulcer, sleep problems, redness of face, awareness of heartbeat, effects on hearing, hyperacusis. More than 1 AE: Interven: 2.0% Cntrl: 1.6%
Johnson, ²⁴ 1993 United States	Baseline sample: Total n = 40 Interven n = 20; Cntrl n = 20 Setting: University clinic Mean age: NR Gender: NR Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: >1 year Severity of tinnitus: Constant and not fluctuant in nature, sufficient severity to disrupt daily activities (greater than 600 on the disability sub-scale of the IOWA THQ Number of dropouts: Interven n = 3, Cntrl n = 1 Reasons for dropouts: Excessive drowsiness (2); not attend 2nd appointment (1); noncompliance (1) Audiological factors: NR Comorbidities: NR	Interven: Alprazolam Subjects given a 9-day supply of Alprazolam, 1 per day, return to the clinic for a reevaluation of their tinnitus. Subjects interviewed for adverse reaction to drugs, and loudness of tinnitus evaluated with synthesizer. If no AE for the first week, received an appropriate amount of medication for the next 23 days and asked to return to clinic. Followup at 21 days, if tolerated well, were given a final supply of the drug for 58 days, and scheduled for a return visit in 56 days. Comparator: Placebo Duration of treatment: 12 weeks Number of follow-ups: 3 (1, 4, 12 weeks) Duration of study: NR	Loudness (VAS)	Of the 17 patients receiving alprazolam, 13 (76%) had a reduction in the loudness of their tinnitus when measurements were made using a tinnitus synthesizer and a visual analog scale. Alprazolam is a drug that will provide therapeutic relief for some patients with tinnitus. Adverse Events: excessive drowsiness (2); mild withdrawal symptoms (1); more dreams (4); unfocussed (1)

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Mazurek, ⁹⁷ 2009 Germany	Baseline sample: Total n=42 Setting: Tinnitus Centre Mean age (SD): Total=49.0 y (10.2) Gender: 71.4% male Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: > 3 months Severity of tinnitus: "chronic" (excluded acute or intermittent) Number of dropouts: Interven=5; Cntrl=2 Reasons for dropouts: drug-related adverse events: Interven=4; Cntrl=1; poor compliance: Interven=1; Cntrl=1 Audiological factors: NR Comorbidities: NR	Vardenafil Interven: 10 mg vardenafil administered orally twice a day over a period of 12 week, dosing interval approx.12 hours. Non-medicated follow-up for another 4 weeks. Comparator: Matching placebo tablets administered orally twice a day over a period of 12 week Duration of treatment: 12 weeks Number of follow ups: Measured at baseline (V2), 4 weeks into treatment (V3), at the end of treatment (V4), and 4 weeks after treatment (V5). Duration of study: 16 weeks	G-QOL (SF-36) TS-QOL (TQ) Sleep (TQ-subscale)	Vardenafil had no superior efficacy over placebo in the treatment of chronic tinnitus during this study. Within- and between-groups differences on the TQ were clinically not relevant. There was a tendency on the TQ subscales for minor deteriorations under Vardenafil medication. All differences in changes from baseline were statistically not significant. Adverse Events: There were no serious or fatal AEs. 6 subjects (28.5%) in the Vardenafil group reported drug-related AEs of headache, diarrhea, nasal congestion or prolonged penile erection
Meeus, ⁹⁸ 2011 Belgium	Baseline sample: Total n = 35 Interven n = 13; Cntrl n = 15 Setting: Multidisciplinary Tinnitus Clinic Mean age (SD): 55.4y (9.1) Int: 57.9y ; Cntrl: 53.2y Gender: 89.3% male Int: 76.9%male; Cntrl 100% male Presumed etiology of tinnitus: unilateral or bilateral tinnitus Duration of tinnitus: > 3m Severity of tinnitus: primary complaint of chronic tinnitus Number of dropouts: 7 Reasons for dropouts: NR Audiological factors: normal MRI pontine angle Comorbidities: none	Double-blind crossover trial – data extracted from end of first period only Interven: Additional effect of Deanxit (Flupentixol 0.5 mg + melitracen 10 mg) on clonazepam (Rivotril) 1 mg Comparator: Placebo Duration of treatment: 3 weeks Number of followups: 1 week washout, switch to treatment Duration of study: NR	Loudness (VAS) Sleep (TQ-sub) Depression (BDI) TS-QOL (TQ*, VAS)	Significant tinnitus reduction was seen after intake of the combination clonazepam-Deanxit, whereas no differences in tinnitus could be demonstrated after the administration of clonazepam-placebo. This was true for all patients according to the following parameters: time patients are annoyed by the tinnitus (p = 0.026) and the VAS for tinnitus annoyance (p = 0.024). Adverse events: extrapyramidal syndromes and tardive dyskinesia are known side effects of Deanxit – <u>not</u> observed in this study population

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Piccirillo, ¹⁰¹ 2007 United States	Baseline sample: Total n=115 Interven=70; Cntrl=65; Setting: Dept of Otolaryngology Mean age (SD): NR Gender: Interven: 35.6% male; Cntrl: 44.6% males Presumed etiology of tinnitus: NR Duration of Tinnitus: >6m Severity of tinnitus: Sufficient to disrupt daily activities, THI score ≥38 Number of dropouts: Interven: 11; Cntrl: 9 Reasons for dropouts: Lack of results(9); Nausea(3); Weight gain(2); sleep disturbance(2); Dizziness(1); Other(2) Audiological factors: NR Comorbidities: TMJ Interven: 86%; Cntrl: 77%	Gabapentin (Neurontin) Interven: Patients in gabapentin arm received gradually titrated dosages of gabapentin (week 1, 900 mg/d; week 2, 1800 mg/d; week 3, 2700 mg/d; and week 4, 3600 mg/d). All subjects were provided an equal number of capsules (300 mg each) and instructed to follow a dosing schedule of 3 times per day. If intolerable adverse reactions occurred, the dosage was decreased in 1-dose (300 mg) steps until the drug could be tolerated. The dose established during the titration period was maintained throughout the additional 4 week fixed-dose period afterwards Comparator: Placebo Duration of treatment: 8 weeks Number of follow-ups: 2 (4 weeks; 8 weeks) Duration of study: 8 weeks	TS-QOL (THI)	The change among the 59 subjects randomized to the gabapentin arm was 11.3 and the change among the 56 subjects in the placebo arm was 11.0. The difference was 0.03 (95% confidence interval, -5.5 to 6.2; <i>P</i> =.91). The response to gabapentin, as measured by the THI score, does not reflect a true effect. Adverse Events: 9/153 (7%) withdrew owing to AEs. Nausea (3); Weight gain (2); Sleep disturbance (2); dizziness (2). All AEs ceased on discontinuation of the study medication.

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Rejali, ¹⁰³ 2004 United Kingdom	<p>Baseline sample: Total n = 66 Interven n = 33; Cntrl n = 33 Setting: Otolaryngology clinic Mean age (SD): Interven: 60 y (11.4); Cntrl: 59 y (10.4) Gender: Interven: 55% male; Cntrl: 59% male Presumed etiology: noise exposure (55%); middle ear disease (22%); idiopathic (43%) Duration of tinnitus: Duration of tinnitus: Interven: 4.4 y; Cntrl: 5.9 y</p> <p>Severity of tinnitus: main complaint Number of dropouts: 6 Int n = 2; Cntrl n = 4 Reasons for dropouts: Death from a co-existing condition (Int=1); Loss to follow-up (Int=1; Cntrl=2); co-existing illnesses (Cntrl=2) Audiological factors: active middle or external ear disease excluded Comorbidities: NR</p>	<p>Ginkgo Biloba Interven: Patients received 120 mg once daily sustained release formulation of G. biloba Comparator: Placebo</p> <p>Duration of treatment: 12 weeks Number of follow-ups: 1 Duration of study: NR</p>	<p>TS-QOL (THI) G-QOL (GHSI)</p>	<p>Ginkgo biloba does not benefit patients with tinnitus</p> <p>Adverse Events: diarrhea (6% in placebo and 3% in active group) and headache (3% in each group).</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Robinson, ¹⁰⁵ 2005 United States	<p>Baseline sample: Total: n = 115; Interven n = 57; Cntrl n = 58 Setting: Otolaryngology clinic</p> <p>Mean age: 57 y Gender: 58% male Presumed etiology of tinnitus:</p> <p>Duration of tinnitus: >6m Severity of tinnitus: NR Number of dropouts: 26 Interven n = 17; Cntrl n = 5 Reasons for dropouts: adverse events (side effect, perceived increase in tinnitus) Audiological factors: NR Comorbidities: Major depression (n=1) Number of dropouts: 26 (Interven=17; Cntrl=5) Reasons for dropouts: adverse events (side effect, perceived increase in tinnitus)</p>	<p>Paroxetine: Treatment 10 mg of paroxetine (or placebo) per day for the first week. Dose increased to 20 mg per day for 2 weeks. Dose was increased in 10-mg increments every 2 weeks to a maximum of 50 mg per day.</p> <p>Comparator: Placebo</p> <p>Duration of treatment: 100 days Number of follow-ups: 1 (1 month post- treatment) Duration of study: (mean) 100 days</p> <p>NOTE: 21 participants who withdrew from the study had their last observation carried forward, resulting in a total of 115 participants with follow-up data, used in the ITT analysis</p>	<p>Depression (HADS-D, BDI*)</p> <p>Anxiety (HADS-A, BAI*)</p> <p>TS-QOL (THQ*, Likert 0 to 7)</p> <p>Sleep (PSQI)</p> <p>G-QOL (QWB)</p>	<p>Majority of individuals did not benefit from paroxetine in a consistent fashion.</p> <p>Adverse Events: Significantly more participants in the paroxetine group (n =17) dropped out because of adverse events than those in the placebo group (n =5), p < .05). Significantly more participants in the paroxetine group reported moderate or severe sexual dysfunction, drowsiness, and dry mouth than in the placebo group at follow-up.</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Sharma, ¹⁰⁶ 2012 India	<p>Baseline sample: Total n = 40 Setting: Outpatient Department of ENT Hospital Mean age (SD): 53 years Gender: NR</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: NR Severity of tinnitus: NR Number of dropouts: 5 Reasons for dropouts: worsening of condition (n=2); left treatment at crossover and could not complete the study (n=3) Audiological factors: varying degrees of sensorineural hearing loss; 65% of patients had bilateral hearing loss; 35% had bilateral tinnitus Comorbidities: NR</p>	<p>Acamprosate</p> <p>Interven: tab. acamprosate 333 mg 1 tab TID for 45 days; then washout period of 7 days; crossed over to matched placebo 1 tab orally TID for next 45 days Cntrl: matched placebo 1 tab TID for next 45 days; then washout period of 7 days; crossed over to tab acamprosate 333 mg 1 tab orally TID for 45 days Comparator: Placebo</p> <p>Duration of treatment: 45 days Number of follow-ups: 3 (45 days, 7 day washout, 45 day) Duration of study: NR</p>	<p>G-QOL (Subjective) Loudness (VAS)</p>	<p>The drug had shown a statistically significant improvement in reducing the tinnitus score in 92.5% of the patients and placebo with an improvement in 12.5% of the patients.</p> <p>Adverse Events: The drug was well tolerated without any serious drug reactions</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Sullivan, ¹⁰⁷ 1993 United States	<p>Baseline sample: Total n = 117: Interven n = 63, Cntrl n = 54 Setting: University otolaryngology clinic Mean age (SD): 62.1 y (8.0) Gender: 52% male Interven: 61% male; Cntrl: 42% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: ≥ 6 months Severity of tinnitus: sufficient severity to disrupt daily activities (score ≥600 THQ disability subscale) Number of drop outs: Interven n = 14; Cntrl n = 11 Reasons for dropouts: Interven: Anticholinergic side effects, sedation; Cntrl: Unsatisfactory therapeutic response and scheduling conflicts Audiological factors: Treatable otologic disorder related to the tinnitus excluded Comorbidities: 28 participants had current major comorbid depression and 54 were depression-NOS subjects</p>	<p>Nortriptyline Intervention: Treatment initiated at 25 mg at bedtime and titrated upward 25 mg per week. When therapeutic or side effects were evident or when 100 mg was reached, blood level was assessed. Dosage adjusted to a therapeutic level between 50 and 150 mg/mL and maintained there for 6 weeks. Comparator: Placebo</p> <p>Nortriptyline and placebo groups received same number of capsules and same titration protocol.</p> <p>Duration of treatment: 12 weeks Number of follow ups: 1 Duration of study: NR</p>	<p>Depression (HDS)</p> <p>Anxiety (Sheehans' Disability Scale)</p> <p>TS-QOL (IOWA*, Likert scale)</p>	<p>The antidepressant Nortriptyline decreases depression, functional disability, and tinnitus loudness associated with severe chronic tinnitus.</p> <p>Separate analysis demonstrates that decreases in tinnitus disability closely parallel decreases in depression severity.</p> <p>Adverse Events: anticholinergic side effects and sedation (n=11)</p>

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Topak, ¹⁰⁹ 2009 Turkey	Setting and subject recruitment: Hospital Baseline Sample: Total n=69 Mean age (SD): Interven: 49.9 y; Cntrl: 55.3 y Gender: Interven: 66.7% male; Cntrl: 58.6% male Presumed etiology of tinnitus: Subjective tinnitus of cochlear origin Duration of tinnitus: NR Severity of tinnitus: Only subjects for whom drug treatment had failed Number of dropouts: 11 Reasons for dropouts: Failed to return for follow-up Audiological factors: Patients with sudden sensorineural hearing loss excluded Comorbidities: NR	Methylprednisolone (by intratympanic injection). Patients were randomized to receive one of two treatments: 0.3 to 0.4 ml intratympanic injections of either a 6.25mg methylprednisolone solution or placebo (saline solution). The treatment protocol comprised 3 intratympanic injections, 1 per week for 3 weeks. Comparator: Placebo Duration of treatment: 3 weeks Number of follow ups: 1 Duration of study: 30 months	TS-QOL (TSI) Loudness (Self-rated)	No significant post-treatment changes in the tinnitus severity index individual and total scores were observed in either group. The results of this study indicate that intratympanic methylprednisolone has no benefit, compared with placebo, for the treatment of subjective tinnitus of cochlear origin refractory to medical treatment. Adverse Events: pain during injection, vertigo, a burning sensation around the ear and in the throat, and a bitter taste
Westerberg, ¹¹ 1996 United States	Baseline sample: Total n = 63 Interven n = 31; Cntrl n = 32 Setting: ear institute Mean age (SD): Total: 51.2 y Gender: 57% male Interven: 58% male; Cntrl: 56% male Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: NR Severity of tinnitus: NR Number of dropouts: 11 Reasons for dropouts: side effects (n=9); unknown (n=2) Audiological factors: Only constant, non- pulsatile included Comorbidities: NR	Baclofen vs Placebo Baclofen: Three weeks of baclofen (10 mg BID for 1 week, 20 mg BID 2 nd week and 30 mg BID 3 rd week) were given to drug group. Drug was tapered before discontinuation Comparator: Placebo designed to mimic baclofen capsules in route, schedule appearance and taste Duration of treatment: 3 weeks Number of follow-ups: 1 (3 weeks) Duration of Study: NR	TS-QOL (THI) Self-reported Loudness (Subjective 0- 10)	Reports of subjective improvement occurred in only 9.7% of the baclofen vs 3.4% of the placebo groups (NS). Adverse Events: 26% withdrawals from the baclofen arm due to AEs. None were severe or life threatening and all resolved with stopping the medication or by study's end.

Table E1. Pharmacological or food supplement interventions and outcomes (n=16) (continued)

Author Year Setting	Population	Intervention	Outcome Measures	Results
Zoger, ¹¹⁴ 2006 Companion: Holgers, ⁹⁰ 2011 Sweden	Baseline sample: Total n = 76; Interven n = 38; Cntrl n = 38 Setting: Audiology department, university hospital Mean age (SD): Interven: 40 y; Cntrl: 46 y Gender: Interven: 51.7% male; Cntrl: 61.8% male Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: NR Severity of tinnitus: major complaint Number of drop outs: Interven n = 9; Cntrl n = 4 Reasons for drop outs: Interven; A/E (2), moved (1), stress (2), other (4) Cntrl: changed psychiatric condition (2), moved (1); other (1) Audiological factors: Pure-tone averages better than 50dB HL in the worse hearing ear; positive answer on at least one of NHP items Comorbidities: excluded psychiatrically severe condition in need of acute treatment	Sertraline Interven: During the first week, 25mg/d of sertraline; 50 mg/d thereafter. To alleviate an expected initial worsening of psychological distress, all patients offered oxazepam 10mg during first 2 weeks of the study. Limit 3 tablets of oxazepam 10mg daily to maximum of 25 tablets Comparator: Placebo Duration of treatment: 16 weeks Number of follow-ups: 2 (16 weeks and 28 weeks) Duration of study: 28 weeks All patients were offered an open trial of sertraline at week 16 for another 12 weeks (post-data is taken before crossover portion of this study).	TS-QOL (TSQ*, VAS) Loudness (VAS) Anxiety (HAS*, CPRS-S-A, PGWB sub) Depression (HDS*, CPRS-S-A, PGWB sub) G-QOL ⁹⁰ (PGWB)	Individuals in the Interven condition who completed the post-assessment experienced a significant reduction in tinnitus distress from pre-Interven to post-Interven (p =.0001]. The between-groups difference in the rates of reliable change, although in the hypothesized direction, was not statistically significant (p =.15). Adverse Events: Sexual side effects (1 Interven; 2 Cntrl)

*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Abbreviations: A/E = Adverse events; AMT = active motor threshold; CBT = cognitive behavioral treatment; ENT = ear, nose and throat; grp = group; G-QOL = global quality of life; HADS = Hospital Anxiety and Depression Scale; HDS = Hamilton Depression Rating Scale; interven = intervention; month = month; N/A = not applicable; NR = not reported; QOL = quality of life; RCT = randomized controlled trial; SD = standard deviation; TCT = Tinnitus Coping Therapy; THI = Tinnitus Handicap Inventory; TMJ = temporal mandibular joint; TS = tinnitus specific; TSQ = Tinnitus Severity Questionnaire; VAS = visual analog scale; week = week; WLC = wait list Cntrl; yr = year

Table E2. Medical interventions and outcomes (n=11)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Anders, ⁷³ 2010 Czech Republic	<p>Baseline sample: Total n = 52; Interven n = 26; Cntrl n = 26 Setting: Outpatient Otorhinolaryngology clinic Mean age (SD): Interven: 48.1y (14.86); Cntrl: 50.1y (13.97) Gender: 69% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: > 6 months Severity of tinnitus: Uni- or bilateral tinnitus according to KD-10, no response to >3 months of pharmacological treatment Number of dropouts: 10 Reasons for dropouts: Treatment n = 4; worsening of tinnitus (2); adverse events(2) Cntrl n = 6; lack of efficacy (3); adverse events (2); unknown (1) Audiological factors: Included age-adjusted normal sensorineural hearing. Excluded profound hearing loss or Meniere's disease Comorbidities: NR</p>	<p>Repetitive Transcranial Magnetic Stimulation (rTMS) Patients were treated with either real or sham low frequency rTMS over a period of 2 weeks. Blinding design applied.</p> <p>Comparator: Placebo</p> <p>Duration of treatment: 2 weeks Number of follow ups: 4 Duration of study: 6 months</p>	TS-QOL (THI*, TQ-mod, VAS)	<p>The ability to reduce the symptoms of the tinnitus appeared in both randomized groups immediately after the 1 Hz rTMS and sham stimulation phase. There was a significant reduction in both groups of the tinnitus total score on the Tinnitus Handicap Inventory (THI) (real rTMS p=0.00t; sham rTMS p=0.049). Reduction of symptoms as evaluated using the TQ was significant compared to baseline in the real rTMS group at week 2, 6 and 14 (p=0.003; p=0.024; p=0.022).</p> <p>Real 1 Hz rTMS treatment was capable of significantly reducing the total baseline score of basic scales that measure tinnitus severity. Important for patients with long-term symptoms resistant to pharmacological treatment.</p> <p>Adverse Events: unacceptable pain in stimulation area, headache, lack of efficacy and subjective worsening of tinnitus</p>

Table E2. Medical Interventions and outcomes (n=11) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Chung, ⁷⁹ 2012 China	<p>Baseline sample: Total n = 22 Intervention n = 12 Cntrl n = 10 Setting: University medical Hospital Total Mean age: 52.96 (range 20-76 yrs) Gender: Int 91.6% male Cntrl 90.0% male</p> <p>Presumed etiology of tinnitus: Duration of tinnitus: : Int range 0.5 to 20 years Cntrl: 2 to 10 years Severity of tinnitus: Mean score on TQ and THI Number of dropouts: 0 Reasons for dropouts: NA Audiological factors: Most subjects had unilateral problems Comorbidities: Excluded subjects with known history of metal implants, head injury, stroke, epilepsy</p>	<p>Intervention: rTMS coil was placed over the auditory cortex with the intensity setting at 80% of the resting motor threshold. Continuous theta-burst rTMS (ctBS) was delivered at a burst frequency of 5 Hz (the theta rhythm in the EEG); each burst consisted of 3 pulses repeated at 50 Hz. We administered 900 pulses (300 bursts) of stimulation once daily for 10 consecutive business days.</p> <p>Comparator: Sham rTMS</p> <p>Duration of treatment: Once daily for 10 consecutive days Number of followups: 1 week and 1 month post treatment. Duration of study: NR</p>	<p>TS-QOL (THI*, TQ)</p> <p>Loudness (VAS)</p>	<p>9/12 patients (75%) in the active-stimulation group reported tinnitus suppression following treatment with rTMS.</p> <p>TQ global scores averaged 8.58 points lower 1 week after treatment, a significant decrease compared to the sham-stimulation group (p <0.01).</p> <p>THI scores were, on average, 8.33 points lower after treatment, which were also significantly lower than those of patients in the sham-stimulation group (p <0.01).</p> <p>Tinnitus loudness also decreased significantly after delivering rTMS. (p<0.05)</p> <p>Adverse Events: No patients experienced sustained side effects after the rTMS treatment.</p>
Cuda, ⁸⁰ 2008 Italy	<p>Baseline sample: Total n = 46 Interven n = 26; Cntrl n = 20 Setting: University Otolaryngolgy clinic Mean age (SD): 56.4y (13.6) Int: 50.3y (9.8); Cntrl: 64.4y (14.1) Gender: 58.7 % male</p> <p>Presumed etiology of tinnitus: non-intermittent subjective tinnitus Duration of tinnitus: mean 6.4 years (8.8) Severity of tinnitus: 'disturbing' > 3 months Number of dropouts: None Reasons for dropouts: NA Audiological factors: 60.9% had no clinically significant hearing impairment Comorbidities: NR</p>	<p>Low Level Laser Stimulation + combined counseling protocol (LLS+). Emission power was 5mW, and the wavelength was 650nm. Patients trained to use the device for 20 minutes per day, each day for 3 months.</p> <p>Comparator: combined counseling protocol with sham LLS (LLS-) Combined Counseling consisted of a combination of hypnotic techniques with relations techniques based on respiration, proprioception and insight</p> <p>Duration of treatment: 3m Number of followups: 10 Duration of study: NR</p>	<p>TS-QOL (THI)</p>	<p>Approximately 61% of irradiated patients had tinnitus severity decreased by one class, in comparison to 35% of the placebo group.</p> <p>This study confirmed a significant difference in the benefit of treatment between the LLS+ and LLS-groups.</p> <p>Adverse events: NR</p>

Table E2. Medical Interventions and outcomes (n=11) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Ghossaini, ⁸⁵ 2004 United States	Baseline sample Total n = 29 Interven n = 15; Cntrl n =14 Setting: NR Age: Range 23 to 83 y Gender: NR Etiology of tinnitus: cause/origin of tinnitus in the study sample varied Duration of tinnitus: 7 months to 60 y Severity of tinnitus: Chronic >6 months Number of dropouts: 2 Reasons for dropouts: Failure to return for post-treatment testing (not included in analysis) Comorbidities: NR	High-Frequency Pulsed Electromagnetic Energy (Diapulse) Patients received 30-minute treatments with the Diapulse device (model D103) 3 times per week for 1 month. Comparator: placebo (deactivated machine) Duration of treatment: 1 month Number of follow-ups: NA Duration of study: NR	TS-QOL (THI*, TMR)	There was no significant change in the pre-treatment and post-treatment audiometric thresholds in either group. There were no significant differences between the pretreatment and post-treatment THI scores or the tinnitus rating scores in either subject group Adverse Events: tingling (Treatment) and worsening of tinnitus (5 Control; 4 Treatment)
Langguth, ⁹⁴ 2008 Germany	Baseline sample: Total n = 32 Interven n = 16; Cntrl n = 16 Setting: Dept. of Psychiatry Mean age (SD): 51.5y (11.6) Int: 52.6y (12.6); Cntrl: 50.3y (10.8) Gender: 71.8% male Int: 81.3% male; Cntrl: 62.5% male Presumed etiology of tinnitus: NR Duration of tinnitus: Int: 10.9y (10.1); Cntrl: 11.7y (10.9) Severity of tinnitus: 'disturbing' tinnitus Number of dropouts: None Reasons for dropouts: NA Audiological factors: normal middle-ear status Comorbidities: all had tried several standard treatment modalities	To investigate whether priming stimulation enhances the efficacy of low-frequency rTMS. Medtronic Interven: Priming protocol (960 stimuli; 6 Hz + 1040 stimuli; 1 Hz) Comparator: standard protocol (2000 stimuli; 1 Hz) Duration of treatment: 10 working days Number of followups: 4 over 13 weeks Duration of study: NR	TS-QOL (TQ)	There was no significant difference between the standard protocol and the protocol involving priming stimulation. Data does not support an enhancing effect of higher frequency priming on low-frequency rTMS in the treatment of tinnitus. Adverse Events: No serious adverse or side effects were observed

Table E2. Medical Interventions and outcomes (n=11) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Marcondes, ⁹⁶ 2010 Spain	Baseline sample: Total n=19 Interven=10 Cntrl=9 Setting: Otorhinolaryngology clinic Mean Age: NR Gender: NR Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: > 3 months Severity of tinnitus: NR Number of dropouts: 1 Reasons for dropouts: 1 participant withdrew consent before treatment began Audiological factors: Hearing lever in tinnitus ears – data presented by ear Comorbidities: NR	Repetitive Transcranial Magnetic Stimulation: 5 sessions of rTMS performed on 5 consecutive days Comparator: Placebo Duration of treatment: 5 days Number of follow ups: 10 Duration of study: 6 months	TS-QOL (THI)	Significant improvement of the tinnitus score in the active rTMS group as compared to sham rTMS for up to 6 months after stimulation. SPECT measurements demonstrated a reduction of metabolic activity in the inferior left temporal lobe after active rTMS. Results demonstrate a significant reduction of tinnitus complaints over a period of at least 6 months and significant reduction of neural activity in the inferior temporal cortex. Adverse Events: no relevant side effects
Mirz, ⁹⁹ 1999 Denmark	Baseline sample: Total n = 50 Interven n = 25; Cntrl n = 25 Setting: otorhinolaryngology clinic Mean age (SD): Interven n = 48.6 y; Cntrl n = 48.7 y Gender: Total: 75.5% male Interven: 64.0% male; Cntrl: 87.5% male Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: Mean 5.5y Severity of tinnitus: Disabling, chronic Number of dropouts: 1 Reasons for dropouts: Unrelated illness Audiological factors: sensorineural hearing loss Comorbidities: NR	Laser Therapy vs Placebo The active laser applied 50mW (cw, 830 nm) over a period of 10 min per session. The laser treatment consisted of three periods of five consecutive days separated by weekends, totaling 15 treatment sessions. Comparator: Placebo – an identical looking laser probe was inactivated by the producer Duration of treatment: 5 week days Number of follow ups: 4 Duration of study:	Anxiety (STAI) Depression (BDI) Loudness (VAS) TS-QOL (THI*, VAS-Ann, VAS-Att)	The results showed only moderate (18%) subjective improvement with no statistically significant differences between the effects of the active laser and placebo treatment. There were no statistically significant differences in pre-post measurements of tinnitus loudness, VAS scores, THI scores, or TCSQ scores for patients treated with active laser compared with those treated with placebo. Adverse Events: No serious untoward adverse or side effects were noticed

Table E2. Medical Interventions and outcomes (n=11) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Plewnia, ¹⁰² 2012 Germany	<p>Baseline sample: Total n = 48 Interven1 (SAC) n = 16 Interven2 (TAC) n = 16 Cntrl (PLC) n = 16 Setting: University Psychiatry and outpatient clinic Department of Otorhinolaryngology Mean age (SD): SAC: 46.4y (13.0); TAC: 55.8y (9.7); PLC: 45.6y (10.3) Gender: SAC 10.5%male; TAC 43.8%male; PLC 50%male</p> <p>Presumed etiology of tinnitus: NR Duration of tinnitus: < 5y chronic tinnitus Severity of tinnitus: NR Number of dropouts: total n = 8; SAC n = 4; TAC n = 2; PLC n= 2 Reasons for dropouts: Tinnitus worsening (4); Patient decision (3); sudden hearing loss (1) Audiological factors: Comorbidities:</p>	<p>4 weeks of bilateral cTBS to the secondary auditory cortex (SAC) and temporoparietal cortex (TAC) Stimulation (cTBS) intensity was standardized at 80% AMT Each stimulation train (40 s) consisted of 600 stimuli applied in bursts of 3 pulses at 50 Hz given every 200 msec (i.e., at 5 Hz). Fifteen minutes after the first 2 trains, a second pair of cTBS trains was given (a total of 2,400 stimuli/day). Patients received cTBS treatment each working day for 4 weeks (20 sessions) the 10–20 EEG electrode placement system was used to localize Brodmann area 39 (TAC: halfway between T5/P3 and T6/P4) and Brodmann area 42/22 (SAC: halfway between T3/C3 and T4/C4). For adequate masking of the patients, sham stimulation (PLC) was performed behind the mastoid. Comparator: sham stimulation (PLC)</p> <p>Duration of treatment: 4 weeks Number of followups: 1 (12 weeks) Duration of study: Feb 2008 to May 2010</p>	TS-QOL (TQ)	<p>Tinnitus severity was slightly reduced from baseline by a mean (SD) 2.6 (8.2) after sham, 2.4 (8.0) after temporoparietal, 2.2 (8.3) after temporal treatment of 16 patients each, but there was no significant difference between sham treatments and temporal (confidence interval [CI] -5.4 to +6.7) or temporoparietal cTBS (CI -5.9 to +6.3) or real cTBS (CI -7 to +5.1).</p> <p>Patients' global evaluation of tinnitus change after treatment did not indicate any effects.</p> <p>Adverse events: Patients reported the following side effects: headache (SAC: 2, TAC: 2, PLC: 3), worsening of tinnitus (SAC: 1, TAC: 2, PLC: 3), increased sensitivity to noise (TAC: 1, PLC: 1), painful local sensation (SAC: 1), and sleep disturbance (SAC: 1). An acute hearing loss associated with increased tinnitus loudness was observed in 1 patient after session 17 (SAC). In this patient, hearing thresholds and tinnitus returned to baseline after 3 weeks.</p>

Table E2. Medical Interventions and outcomes (n=11) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Tass, ¹⁰⁸ 2012 Germany	<p>Baseline sample: Total n=63 Interven (4 groups) G1 n = 22; G2 n = 12; G3 n = 12; G4 n = 12 Cntrl (G5) n = 5 Setting: 2 treatment centers in Germany Mean age (SD): >18 G1: 45.7 (10.8); G2 47.7 (5.6); G3 50.0 (14.7); G4 50.3 (11.8); G5 57.6 (6.3) Gender: G1: 72.7% male; G2: 83.3% male; G3: 50.0% male; G4: 75.0% male; G5: 60.0% male</p> <p>Presumed etiology of tinnitus: chronic tonal tinnitus Duration of tinnitus [years – Mean (SD)]: all >6 months G1: 5.7 (5.1); G2: 6.6 (6.0); G3: 5.4 (3.5); G4: 7.9 (9.8); G5: 11.3 (5.6) Severity of tinnitus: chronic Number of dropouts: 0 Reasons for dropouts: N/A Audiological factors: Morbus Meniere, TMJ, psychiatric disorders and objective tinnitus excluded Comorbidities: NR</p>	<p>Acoustic Coordinated Reset (CR) neuromodulation: 4 stimulation groups. For G1, G3 and G4 four tones (top, f1 to f4) are grouped around the tinnitus frequency (ft). G3 differs only in repetition rate F being adapted to the individual EEG δ-band peak. For G2 each CR cycle is formed by a varying composition of four tones (dark green: active) chosen out of twelve tones (middle, f1 to f12) surrounding ft.</p> <p>Comparator: Placebo stimulation (G5) is formed similar to G1 using a down-shifted stimulation-frequency fp ($fp = 0.7071 \cdot ft / (2n)$, fp within [300 Hz, 600 Hz]) outside the synchronized tinnitus focus.</p> <p>Duration of treatment: G1 to G3 received stimulation for 4 to 6 hours every day for 12 weeks applied either continuously or split into several sessions not shorter than 1 hour G4 and G5 all received stimulation for 1 hour max. every day</p> <p>Number of followups: 1,4,8, 12 and 16 weeks after beginning of treatment and every 4 weeks during optional 24 week LTE</p> <p>Duration of study: NR</p>	<p>TS-QOL (TQ*, VAS) Loudness (VAS)</p>	<p>Strong and significant reduction of VAS loudness in G1 and G3 in the on-stimulation condition ($p \leq 0.01$) G1 also significant compared to placebo (G5) ($p < 0.05$)</p> <p>A reduction of at least 6 TQ points was obtained in 75% of patients with a mean TQ reduction of 50% among responders.</p> <p>Adverse events – 15 AEs: 13 AEs during blinded phase, 2 AEs in LTE. 2 SAEs not associated with treatment were reported; All other AEs were of mild to moderate intensity and none was permanent. 8 AEs were judged to be treatment related of which 3 AEs were associated with a transient increase of tinnitus loudness</p>

Table E2. Medical Interventions and outcomes (n=11) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Teggi, ³¹ 2009 Italy	Baseline sample Total n = 60 Interven: n = 30; Cntrl n = 30 Setting: ENT department Mean age (SD): Interven: 51.6y (11.3); Cntrl: 53.1y (12.9) Gender: Interven: 59.2% male; Cntrl: 51.2% male Presumed etiology of tinnitus: NR Duration of Tinnitus: NR Severity of tinnitus: NR Number of dropouts: Interven n = 3; Cntrl n = 3 Reasons for dropouts: familial reasons (4), increase in tinnitus loudness (2) Audiological factors: NR Comorbidities: NR	Laser Therapy All patients instructed to perform laser therapy with the TinniTool soft laser at home for 20 min a day for a period of 3 months; patients in the first group (group L) received an active laser Comparator: Placebo - a dummy laser (group C). Duration of treatment: 3 months Number of follow ups: 1 Duration of study: NR	TS-QOL (THI) Loudness (VAS)	No statistical difference was detected between the 2 groups in the THI total score (p = 0.97), and the functional (p = 0.89), emotional (p = 0.89) and catastrophic (p = 0.89) subscales. VAS for self-perceived loudness of the tinnitus showed no difference between the groups (p = 0.69). Soft laser therapy demonstrated no efficacy as a therapeutic measure for tinnitus in this report. Adverse Events: subjects with migraine presenting hyperacusis (Treatment = 4; Control = 2). Increase in loudness (Treatment = 1; Control = 1)
Vilholm, ¹¹⁰ 1998 Denmark	Baseline sample Total n = 54 Interven n = 29; Cntrl n = 25 Setting: Department of Audiology Mean Age (SD): 53.1 y Gender: Int: 68.9% male; Cntrl: 60.0% male Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: ≥ 1 yr Severity of tinnitus: Severe treatment-resistant tinnitus Number of dropouts: 0 Reasons for dropouts: N/A Audiological factors: NR Comorbidities: NR	Acupuncture vs Placebo Acupuncture group treated with traditional Chinese acupuncture of 25 treatment sessions over 2 months. Sessions distributed over 3 treatment periods of 10, 5 and 10 treatments separated first by a pause of one week, and then by a pause of two weeks. Treatment given each day for 30 minutes. Comparator: Placebo group treated with placebo acupuncture. Duration of treatment: 4 months Number of follow ups: 2 Duration of study: NR	TS-QOL (VAS-Ann*, VAS-Awr) Loudness (VAS)	No statistically significant differences were found between the acupuncture group and the placebo group. Adverse Events: NR

*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Abbreviations: A/E = Adverse events; AMT = active motor threshold; CBT = cognitive behavioral treatment; ENT = ear, nose and throat; G1 to G5 = group; G-QOL = global quality of life; HADS = Hospital Anxiety and Depression Scale; interven = Intervention; month = month; N/A = not applicable; NR = not reported; QOL = quality of life; RCT = randomized Controlled trial; SD = standard deviation; TCT = Tinnitus Coping Therapy; THI = Tinnitus Handicap Inventory; TMJ = temporal mandibular joint; TS = tinnitus specific; TSQ = Tinnitus Severity Questionnaire; VAS = visual analog scale; week = week; WLC = wait list Cntrl; yr = year

Table E3. Sound treatment/technologies intervention and outcomes (n=5)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Davis, ⁴⁶ 2007 Australia	<p>Baseline sample: Total n = 35 Stage1 n = 16; Stage2 n = 19 Setting: Clinic Mean age (SD): 58.5y(13.4) Stage1: 61.3y(8.9); Stage2: 56.1y(16.2) Gender: 74%male</p> <p>Presumed etiology of tinnitus: NR Duration of tinnitus: 11.0y (11.3) Severity of tinnitus: moderate to severe Number of dropouts: 1 Reasons for dropouts: NR Audiological factors: decreased sound tolerance Comorbidities: NR</p>	<p>Participants were provided with a high fidelity personal sound player with earphones and an acoustic stimulus that had been spectrally modified according to their individual audiometric profile. They were instructed to use the acoustic stimulus for at least 2 hr per day, particularly at those times when their tinnitus was usually disturbing. Each group had equal amounts of clinician time for education, monitoring, and support. Complete covering of perception initially, then intermittent perception (Stage2)</p> <p>Comparator: intermittent perception throughout (Stage1)</p> <p>Duration of treatment: 12m Number of followups: 2,4,6 and 12 m Duration of study: NR</p>	<p>TS-QOL (TRQ, VAS)</p> <p>Loudness (VAS)</p>	<p>Improvements increased with time over the first 6 months of therapy, at which time 91% of all subjects across the two groups reported an improvement in tinnitus disturbance (as measured by the TRQ) of at least 40%, with a mean improvement of 65%.</p> <p>Inter-group differences were not statistically significant measuring tinnitus disturbance.</p> <p>Adverse events: NR</p>
Dineen, ^{82,83} 1999, 1997 Australia	<p>Baseline sample: Total n = 96 Group I: n = 28; Group ID: n = 20 Group IR: n = 28; Group IDR: n = 20 Setting: Hearing Clinic, University Mean age (SD): 54.37y (13.86) Gender: 66.1% male</p> <p>Presumed etiology of tinnitus: NR Duration of tinnitus: NR Severity of tinnitus: NR Number of dropouts:25 Group I: 10 (36%); Group ID: 7 (35%) Group IR: 5 (18%); Group IDR: 3 (15%) Reasons for dropouts: 12 returned questionnaires, 2 in hospital; 2 away; 5 couldn't attend clinic; 3 tinnitus not a sufficient problem Audiological factors: NR Comorbidities: NR</p>	<p>Tinnitus management training designed to characterize common components of published tinnitus management programs</p> <p>Group I: Information Only Group ID: Information plus long-term low-level white noise (LTWN) – Starkey TM devices, 2 3-hour sessions Group IR: Information plus relaxation therapy Group IDR: Information plus LTWN plus relaxation</p> <p>Duration of treatment: 2.5 hours per subject Number of followups: 3m, 12m Duration of study: NR</p>	<p>TS-QOL (TRQ, VAS)</p> <p>Loudness (VAS)</p> <p>G-QOL (DSP)</p>	<p>Subjects who initially had low ability to cope with tinnitus and preferred a more active coping style reported significantly greater benefit from LTWN stimulation than subjects whose primary approach to coping was to regulate the emotional impact of tinnitus.</p> <p>Adverse Events: NR</p>

Table E3. Sound treatment/technologies intervention and outcomes (n=5) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Hiller, ⁸⁹ 2005 Germany Study 1	<p>Baseline sample: Total n = 136 Int1 (CBT+NG) n = 33; Cntrl1 (CBT only) n = 33 Setting: Outpatient Department, University Mean age (SD): Int1 (CBT+NG): 51.0y (13.2); Cntrl1 (CBT only): 51.4y (10.9) Gender: Int1 (CBT+NG): 68% male Cntrl1 (CBT only): 41% male</p> <p>Presumed etiology of tinnitus: > 25% had sudden hearing loss Duration of tinnitus: at least 6 months Severity of tinnitus: chronic Number of dropouts: Int1 (CBT+NG)= 2; Cntrl1 (CBT only)= 4 Reasons for dropouts: external reasons; insufficient motivation; unknown Audiological factors: NR Comorbidities: NR</p>	<p>CBT: subjects score 40 or more on TQ (severe), training consists of 10 120- minute sessions. Treatment was strictly manualized.</p> <p>All therapies conducted by two clinical psychologists</p> <p>Int1 = CBT + Noise generator Cntrl1 = CBT only</p> <p>Duration of treatment: up to 10 weeks Number of followups: 6, 18m Duration of study: NR</p>	<p>TS-QOL (TQ, T-Cog)</p> <p>Loudness (VAS)</p> <p>Anxiety (WI)</p>	<p>No additive effects due to the NGs could be demonstrated.</p> <p>Adverse Events: NR</p>
Hiller, ⁸⁹ 2005 Germany Study 2	<p>Baseline sample: Total n=136 Int2 (TE + NG)= 34; Cntrl2 (TE only) = 36 Setting: Outpatient Department, University Mean age (SD): Int2 (TE + NG)= 52.5y (15.3) Cntrl2 (TE only) = 45.2y (14.1) Gender: Int2 (TE + NG)= 52% male Cntrl2 (TE only) = 61% male</p> <p>Presumed etiology of tinnitus: > 25% had sudden hearing loss Duration of tinnitus: at least 6 months Severity of tinnitus: chronic, Number of dropouts: Int2 (TE + NG)= 3; Cntrl2 (TE only) = 3 Reasons for dropouts: external reasons; insufficient motivation; unknown Audiological factors: NR Comorbidities: NR</p>	<p>Tinnitus Education (TE): patients with mild to moderate distress as scored by the TQ – abridged version of CBT 4 90-minute weekly sessions</p> <p>All therapies conducted by two clinical psychologists</p> <p>Int2 = TE + Noise generator Cntrl2 = TE only</p> <p>Duration of treatment: up to 4 weeks Number of followups: 6, 18m Duration of study: NR</p>	<p>TS-QOL (TQ, T-Cog, VAS, Diary)</p> <p>Loudness (VAS)</p> <p>Anxiety (WI)</p> <p>G-QOL (SCL-90R, PSDI)</p>	<p>No additive effects due to the NGs could be demonstrated.</p> <p>Adverse Events; NR</p>

Table E3. Sound treatment/technologies intervention and outcomes (n=5) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Parazzini, ¹⁰⁰ 2011 Italy, United States	Baseline sample: Total n=91 Interven (OE-HA) n=49; Cntrl (SG) n=42 Setting: Tinnitus clinics in Milan, Baltimore Mean age (SD): 38.8y (1.9) Gender: 51/91 (56%) male Int: 57.1%male; Cntrl: 54.7% male Presumed etiology of tinnitus: bilateral symmetrical hearing loss Duration of tinnitus: 69.5m (9.4) Severity of tinnitus: NR Number of dropouts: 10 Reasons for dropouts: NR Audiological factors: borderline between category 1 and category 2 (according to the Jastreboff classification) with HL ≤25 dB at 2kHz and HL ≥25 dB at frequencies >2kHz Comorbidities: No participant treated with TRT before; No previous use of hearing aids	TRT with open hearing aids (OE-HA) Comparator: TRT with sound generator (SG) Duration of treatment: 1 year Number of followups: 3 (3m, 6m, 12m) Duration of study: NR	G-QOL (VAS) TS-QOL (THI) Loudness (subjective)	TRT was equally effective with sound generator or open ear hearing aids: they gave basically identical, statistically indistinguishable results Adverse Events: NR

*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Abbreviations: A/E = Adverse events; AMT = active motor threshold; CBT = cognitive behavioral treatment; DSP = Derogatis Stress Profile; ENT = ear, nose and throat; grp = group; G-QOL = global quality of life; HADS = Hospital Anxiety and Depression Scale; intervention = Interven; month = month; N/A = not applicable; NR = not reported; QOL = quality of life; RCT = randomized Controlled trial; SD = standard deviation; TCT = Tinnitus Coping Therapy; THI = Tinnitus Handicap Inventory; TMJ = temporal mandibular joint; TRQ = Tinnitus Reaction Questionnaire; TS = tinnitus specific; TSQ = Tinnitus Severity Questionnaire; VAS = visual analog scale; week = week; WI = Whiteley Index; WLC = wait list Cntrl; yr = year

Table E4. Psychological/behavioral intervention and outcomes (n=19)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Abbott, ⁷¹ 2009 Australia	<p>Baseline Sample: Total n = 56; Interven n = 32; Cntrl n = 24 Setting: Internet in 23 industrial settings, Mean Age (SD): Interven: 50.5 y (9.5); Cntrl: 48.7 y (8.6) Gender: Interven: 96% male Cntrl: 83% male</p> <p>Presumed etiology of tinnitus: idiopathic Duration of tinnitus: > 3 months Severity of tinnitus: NR Number of dropouts: Interven N=4; Cntrl=1 Reasons for dropouts: most indicated withdrawal by no response when contacted Audiological factors: NR Comorbidities: NR</p>	<p>Internet-based education Interven: 10 components, presented in six modules, and completed at the rate of one module per week. Modules included homework assignments and weekly diaries submitted electronically. Participants completed daily online registrations 1 week before Interven (pre-assessment) and 1 week immediately after Interven (post-assessment) on VAS (range 0 to 10)</p> <p>Comparator: Information only</p> <p>Duration of treatment: 6 weeks Number of follow ups: 1 Duration of study: June 2006 to March 2007</p>	<p>Depression (DASS-D)</p> <p>Anxiety (DASS-A)</p> <p>Loudness (VAS)</p> <p>Sleep (VAS)</p> <p>G-QOL (WHO-Social)</p> <p>TS-QOL (TRQ*, VAS, OSI-R)</p>	<p>The CBT program was not found to be superior to the information program for treating tinnitus distress.</p> <p>Participants who completed the program generally reported finding most aspects of it useful, but found the sound enrichment, sound sensitivity, and cognitive restructuring tools less useful.</p> <p>Adverse Events: None</p>
Andersson, ⁷⁵ 2005 Sweden	<p>Baseline sample Total n = 23; Interven n = 12; Cntrl n = 11 Setting: web pages and newspaper articles Mean age (SD): 70.1y (3.90) Gender: 52% male</p> <p>Presumed etiology of tinnitus: NR Duration of tinnitus: Mean 13y (12.5) Severity of tinnitus: "problem with tinnitus" as inclusion criteria Number of dropouts: None Reasons for dropouts: N/A Audiological factors: 22% previously fitted with hearing aids Comorbidities: NR</p>	<p>CBT Interven: Sessions covered information about tinnitus, applied relaxation, cognitive restructuring, behavioral activation, positive imagery, sound enrichment, exposure to tinnitus, advice regarding hyperacusis, hearing tactics, and relapse prevention.</p> <p>Comparator: Wait list</p> <p>Duration of treatment: 6 weeks of 2 hour sessions Number of follow-ups: 2 (immediately post-treatment and 3 months post-treatment taken after crossover) Duration of study: 19 weeks</p>	<p>TS-QOL (TRQ)</p> <p>Depression (HADS-D)</p> <p>Anxiety (HADS-A*, ASI)</p>	<p>TS-QOL Results showed statistically significant reductions of tinnitus-related distress. $F(1,21)=6.4$, $p=0.02$</p> <p>CBT was better than no treatment, but the particular aspects of CBT that contributed to the effects can not be established.</p> <p>The findings give some support for the use of group CBT for elderly people with tinnitus.</p> <p>Adverse Events: NR</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Andersson, ⁷⁴ 2002 Sweden	<p>Baseline sample Total n = 117; Interven n = 53; Cntrl n = 64 Setting: web pages and newspaper articles Mean age (SD): Interven: 48.5y (12.3); Cntrl: 47.2y (15) Gender: Interven: 54% male; Cntrl: 52% male</p> <p>Presumed etiology of tinnitus: NR Severity of tinnitus: "severe problem" for which patient has seen GP or ENT Number of dropouts: Interven n = 29; Cntrl n = 16 Reasons for dropouts: Interven: 26 did not finish treatment; 4 incomplete questionnaire; Cntrl: 16 incomplete questionnaire Audiological factors: problems in 68% Comorbidities: sleep problems, anxiety, depression</p>	<p>CBT Interven: Self-help manual constructed following cognitive behavioral principles, consisting of 6 modules (1 module performed per week). Daily diary ratings were included for 1 week before and 1 week following the treatment period.</p> <p>Comparator: Wait list</p> <p>Duration of treatment: 6 weeks Number of follow-ups:1 Duration of study: 1 yr</p>	<p>TS-QOL (TRQ*, VAS-Ann, VAS-Ctrl)</p> <p>Anxiety (HADS-A*, ASI)</p> <p>Depression (HADS-D)</p> <p>Sleep (VAS)</p> <p>Loudness (VAS)</p>	<p>TS-QOL: group effect on pre- vs. post-treatment change score: $t(70)=3.99$, $p=0.002$ ITT analysis: NS</p> <p>No significant differences between the groups were found at either post-treatment ($p = 0.29$) or at the 1-year follow-up ($p= 0.16$).</p> <p>CBT via the Internet can help individuals decrease annoyance associated with tinnitus.</p> <p>Adverse Events: NR</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Biesinger, ⁷⁸ 2010 Germany	<p>Baseline sample Total: n = 40 Interven: n = 20; Cntrl: n = 20 Mean age(SD): Interven: 44.7y (10.9); Cntrl: 39.9y (11.3) Gender: 47.1% male</p> <p>Presumed etiology of tinnitus: Nonsomaterenic tinnitus Duration of tinnitus: >3 months Severity of tinnitus: Main complaint Number of dropouts: Interven: 5; Cntrl: 1 Reasons for dropouts: Missed sessions- job-related, personal, organizational reasons, incomplete data Audiological factors: Normal audiogram (LE 10dB or any frequency) as inclusion criteria Comorbidities: NR</p>	<p>Qigong Therapy is a set of breathing and movement exercises with possible benefits to health through stress reduction and body activity. Qigong contains important principles of modern tinnitus therapy, such as relaxation, reduction of muscle tension, attention distraction, stress reduction, activation, and communication, especially when exercising in groups.</p> <p>Qigong training program for 5 weeks, 2 hrs twice a week under professional Qigong instructor.</p> <p>Comparator: Wait list</p> <p>Duration of treatment: 10 sessions, 5 weeks Number of follow ups: 3 Duration of study: NR</p>	TS-QOL (TBF-12*, VAS)	<p>Qigong was completed by 80% of the assigned patients.</p> <p>Compared with the Cntrl group, Qigong participants experienced improvement in tinnitus severity, as reflected by a significant reduction in both the VAS and the TBF-12 (group x time interaction: $F(3,66)=3.7$, $p=0.015$)</p> <p>In the subgroup of patients with somatosensory tinnitus, Qigong effects were more pronounced, resulting in a highly significant improvement in both scales compared to the waiting-list group.</p> <p>Adverse events: No Qigong related reasons affected participation in the study. No relevant side effects were reported.</p>
Cima, ⁵⁴ 2012 Netherlands	<p>Baseline sample Total: n = 492 Interven n = 245; Cntrl n = 247 Setting: Tinnitus Centre Mean age (SD): Int: 53.74y (11.05); Cntrl: 54.63y (12.02) Gender: Int: 65% male; Cntrl: 61% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: >1 year 70% Severity of tinnitus: primary complaint, 84% with continuous tinnitus Number of dropouts: Interven n=74 (30%); Cntrl n=86 (35%) Reasons for dropouts: NR Audiological factors: 19% with hearing aid; 19% with sound generator Comorbidities: NR</p>	<p>Specialized care of CBT with sound-focused tinnitus retraining therapy. Comparator: Usual Care</p> <p>Duration of treatment: 8 months Number of follow ups: 2 Duration of study: September 2007 and January 2011</p>	<p>G-QOL (HUI)</p> <p>TS-QOL (TQ*, THI)</p> <p>Depression (HADS)</p>	<p>Patients assigned to specialized care improved in health-related QOL during a period of 12 months (between-group difference 0.059, 95% CI 0.025 to 0.094; $p=0.0009$);</p> <p>Decreased tinnitus severity (between group difference -8.062, 95% CI -10.829 to -5.295; $p<0.0001$) and tinnitus impairment (between group difference -7.506, 95% CI -10.661 to -4.352; $p<0.0001$).</p> <p>Specialized treatment of tinnitus based on CBT could be suitable for widespread implementation for patients with tinnitus of varying severity.</p> <p>Adverse Events: Adverse results as a result of treatment or measurements did not occur</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Henry, ⁸⁷ 1998 Australia	<p>Baseline sample Total n = 54 Int Grp1: n = 12; Int Grp2: n = 14 Int Grp3: n = 12; Cntrl: n = 14 Setting: response to radio or newspaper announcements Mean age: 56.3 y (range 35 to 83) Gender: 62% male</p> <p>Presumed etiology of tinnitus: idiopathic Duration of tinnitus: >6 months Severity of tinnitus: primary complaint Number of dropouts: 4 Reason for dropouts: NR Audiological factors: score 17+ on the TRQ Comorbidities: treatment resistant, 72% had subjective hearing loss</p>	<p>CBT ACI - Attention Cntrl and Imagery Training: cognitive coping strategies to help subject learn to shift attention to and from tinnitus and focus on pleasant stimuli – all subjects provided with a written educational manual CR – Cognitive Restructuring – all subjects provided with a written educational manual based on case examples and educational materials ACI+CR – Combined Treatment – condensed version of 2 treatments – subjects provided with treatment and education manuals 3 treatment programs consisted of 8 weekly group sessions lasting 90 minutes</p> <p>Comparator: Wait list Cntrl – treatment provided after 8 weeks</p> <p>Duration of treatment: 8 weeks Number of follow-ups: post-treatment, 6 m Duration of study: NR</p>	<p>Depression (BDI) TS-QOL (TRQ*, THQ handicap, TCSQ coping, TEQ)</p>	<p>The analyses revealed that the combined treatment condition (ACI +CR) showed significantly greater improvement on a measure of psychological distress and achieved a higher clinical response rate compared to the two single treatments. Subjects in the CR condition improved significantly more than the ACI condition on the TRQ ($F(1,46) = 4.47, p < 0.05$) Subjects in the combined ACI + CR condition improved significantly more than those subjects in the ACI condition and CR condition on the TRQ ($F(1,46) = 4.38, p < 0.05$). There were no significant group by time effects for any of the dependent variables at the six-month follow-up. Results were interpreted as supporting the practice of combining the two cognitive approaches.</p> <p>Adverse Events: NR</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Henry, ⁸⁶ 1996 Australia	<p>Baseline sample: Total n = 60, Int Grp1: n = 20, Int Grp2: n = 20, Cntrl: n = 20 Setting: Hospital Mean age: 64.6 y Gender: 86.6% male</p> <p>Presumed etiology of tinnitus: idiopathic Duration of tinnitus: >6 months Severity of tinnitus: score ≥ 17 points on the TRQ; unsuccessful previous treatments Number of dropouts: 0 Reasons for dropouts: NA Audiological factors: no hearing aid, masker or tinnitus suppressive medication previous 6 months Comorbidities: NR</p>	<p>CBT ACI - Attention Cntrl and Imagery Training & CBT vs wait list Treatment groups involved 1 90- minute session per week for six weeks. Treatment conducted in groups of 5 to 7 participants. All psychological treatment was delivered by a clinical psychologist. Int Grp1: Cognitive coping skills training plus education; Int Grp2: Education,</p> <p>Comparator: Wait List Cntrl</p> <p>Duration of treatment: 6 weeks Number of follow ups: 2 Duration of study: 12 months</p>	<p>Depression (BDI)</p> <p>TS-QOL (TRQ*, TEQ, THQ- handicap, TCSQ coping, TCQ awareness)</p> <p>Loudness (Self reported)</p>	<p>TS-QOL: significant reduction in tinnitus distress which was significantly greater when the cognitive coping training was combined with education than when education alone was provided ($F(1,57)=16.19$, $p < 0.01$)</p> <p>Subjects who received the combined cognitive/education intervention demonstrated significantly greater reductions in distress and handicaps associated with tinnitus and engagement in dysfunctional cognitions, than the subjects who received education alone. No significant effects were obtained on measures of depression or loudness.</p> <p>Adverse Events: NR</p>
Henry, ⁸⁸ 2007 United States	<p>Baseline sample Total n = 268 Int Grp1 n = 94, Int Grp2 n = 84, Cntrl n = 90 Setting: Hospital Mean age(SD): IntGrp1: 62.1y (8.9); IntGrp2: 60.8y (9.5); Cntrl: 62.0y (11.3) Gender: IntGrp1: 96.8% male; IntGrp2: 96.4% male Cntrl: 96.7% male</p> <p>Presumed etiology: NR Duration of tinnitus: 87.7% GE 3 y Severity of tinnitus: Sufficiently bothersome to warrant Interven Number of dropouts: IntGrp1 n = 26, IntGrp2 n = 23, Cntrl n = 15 Reasons for dropouts: NR Audiological factors: 93% difficulty hearing at least 'sometimes' Comorbidities: NR</p>	<p>Group Education Counseling (TRT principles) Interven group attended four 1.5 hour group sessions each week conducted by audiologists. Assessed at baseline, and at 1, 6, and 12 months after their last group session. Comparison group (traditional-support) subjects attended four weekly 1.5-hour discussion-type group sessions. Sessions were moderated by the project coordinator. No education was provided in the support group.</p> <p>Comparator: no treatment and traditional support</p> <p>Duration of treatment: 4 weeks Number of follow ups: 3 Duration of study: 12 months</p>	<p>TS-QOL (TSI)</p>	<p>The educational counseling group showed a significant reduction in mean TSI score from baseline to 6 months ($p < 0.001$) and baseline to 12 months ($p < 0.001$).</p> <p>The effect sizes for the educational counseling group were 0.59 at 6 months and 0.45 at 12 months, while the effect sizes for the traditional support and no treatment groups were 0.11 or less at 6 and 12 months.</p> <p>Adverse Events: None</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Ireland, ⁵² 1985 Australia	<p>Baseline sample: Total n =33 Setting: University clinic Mean Age: 55.9 y Gender: 46.6% males Int Grp1: 54.5% males Int Grp2: 44.4% males Cntrl:40.0% males</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: NR Severity of tinnitus: Other traditional treatments not recommended or had failed Number of drop outs: 3 Reasons for drop outs: discontinued treatment Audiological factors: NR Comorbidities: NR</p>	<p>Relaxation Therapy vs wait list Int Grp1: Relaxation training; Int Grp2: Counterdemand, Neutral Demand Cntrl: Wait List Cntrl</p> <p>Duration of treatment: 6 weeks Number of follow ups: 2 Duration of study: NR</p>	<p>Anxiety (STAI)</p> <p>Depression (BDI)</p> <p>Loudness (Self-reported)</p> <p>TS-QOL (Tinnitus interference self-report)</p>	<p>No significant effects for relaxation training were found on any measure. The BDI improved significantly from pretreatment to post-treatment, but the degree of change was equivalent for both treated and untreated groups</p> <p>Adverse Events: NR</p>
Kaldo, ⁹¹ 2007 Sweden	<p>Baseline sample: Total n=72 Interven=34; Cntrl=38 Setting: phone calls and mailouts Mean age (SD): Interven=45.9 y(13.0); Cntrl=48.5 y (15.7) Gender: Interven: 50% male; Cntrl: 47.3% male</p> <p>Presumed etiology of tinnitus: NR Duration of tinnitus: >6 months Severity of tinnitus: Score of 10 or above on TRQ Number of dropouts: 12 Reasons for dropouts: 4 ended treatment prematurely; 3 general reasons. 5 unclear Audiological factors: NR Comorbidities: NR</p>	<p>CBT Self-help book and brief telephone therapy Treatment group: read the self-help book and had 7 weekly phone calls from one of two therapists over a period of 6 weeks (HIGH therapist contact group) Cntrl group: Wait-list; received self-help book and had one initial phone call after treatment group finished (LOW therapist contact group) Measured pre-treatment, post-treatment, extra 6 week post-treatment for LOW group, and follow-up 1 yr after LOW group's post-treatment measurement.</p> <p>Comparator: Wait list</p> <p>Duration of treatment: 6 weeks Number of follow ups: 3 Duration of study: 1 yr</p>	<p>TS-QOL (THI, TRQ*, VAS)</p> <p>Loudness (VAS)</p> <p>Depression (HADS-D)</p> <p>Anxiety (HADS-A)</p> <p>Sleep (ISI)</p>	<p>TS-QOL: group x time interaction: ($F(1,70)=12.4$, $p <0.001$)</p> <p>On the TRQ, in the treatment group, 32% reached the criteria for clinical significance (at least 50% reduction of the TRQ) compared to 5% in the wait-list group.</p> <p>In the treatment group, 32% reached the criteria for clinical significance (at least 50% reduction of the TRQ) compared to 5% in the wait-list group.</p> <p>Adverse Events: NR</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Kaldo, ⁹² 2008 Sweden	<p>Baseline sample: Total n = 51 Interven n = 26; Cntrl n = 25 Setting: Audiology clinic, Internet Mean age (SD): Int: 47.4 (12.9); Cntrl: 45.0 (12.8) Gender: Int 58% male; Cntrl 56% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: Int: 9.9y(13.5); Cntrl: 5.6y (6.1) Severity of tinnitus: primary problem; ≥10 TRQ (Wilson et al., 1991) Number of dropouts: 7 Int n=4; Cntrl n=3 Reasons for dropouts: NR Audiological factors: 33% "Much" or "very much: distressed by hearing deficit Comorbidities: NR</p>	<p>Recruited by advertisements in newspapers, Wait List Cntrl for psychological treatment at the local Dept. of Audiology</p> <p>Internet-administered CBT self-help</p> <p>Comparator: traditional CBT group treatment</p> <p>Both groups used the same treatment manual</p> <p>Duration of treatment: 7 weeks Number of followups: 1 Duration of study: 14 months</p>	<p>TS-QOL (THI, TRQ, VAS)</p> <p>Depression (HADS-D)</p> <p>Anxiety (HADS-A)</p> <p>Sleep (ISI)</p> <p>Loudness (VAS)</p>	<p>Both groups had improved, and there were few differences between them.</p> <p>The effect size for the Internet treatment was $d = 0.73$ (95% CI = 0.16 to 1.30) and for the group treatment was $d = 0.64$ (95% CI = 0.07 to 1.21).</p> <p>The Internet treatment consumed less therapist time and was 1.7 times as cost-effective as the group treatment.</p> <p>Adverse Events: NR</p>
Kröner-Herwig, ⁹³ 1995 Germany	<p>Baseline sample: Total n = 95; TCT1 n = 7; TCT2 n = 8; Yoga n = 9; WLC n = 19 Setting: Dept. of Audiology Mean age (SD): Total: 46.8y (11.5); TCT1: 44.7 y(12.7); TCT2: 48.5 y(10.6); Yoga: 50.0 y (12.6); WLC: 47.3 y (7.9) Gender: TCT1: 57% male; TCT2: 50% male; Yoga: 67% male; WLC: 63% male</p> <p>Presumed etiology of tinnitus: idiopathic Duration of tinnitus: Mean 4.5 y (range 6m to 20y) Severity of tinnitus: >4 on a 10 point scale Number of dropouts: TCT1 n=3; TCT2 n=2; Yoga n=1; WLC n=3 Reasons for dropouts: NR Audiological factors: hearing ability enough to allow communication in a group setting Comorbidities: hearing deficits with 56%</p>	<p>CBT</p> <p>Tinnitus Coping Training: TCT1 and TCT2 to Cntrl for therapist effect – training consisted of Patient Education (1 session); CBT (sessions 2 to 10) Yoga (Hathayoga) – special yogic exercises to foster relaxation and adequate body perception Comparator: Wait List Cntrl (WLC)</p> <p>Duration of treatment: 10- 2 hour sessions Number of followups: end of treatment, 3 month followup Duration of study: 22 weeks</p>	<p>Loudness (Diary)</p> <p>Sleep (Diary, TQ subscale*)</p> <p>G-QOL (TQ, Bef-Skala, Bes-Liste*)</p> <p>Depression (Dep-Skala)</p> <p>TS-QOL (Diary, TQ*)</p>	<p>TS-QOL: reduced psychological impairment German version of the TQ $F(1,32)=4.43$, $p \leq 0.04$</p> <p>Statistical analyses showed effects favoring the TCT treatment in comparison to the Cntrl and yoga treatment. The TCT-treated patients reported more satisfaction with the training than the yoga group.</p> <p>Adverse Events: NR</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Kröner-Herwig, ¹³ 2003 Germany	<p>Baseline sample: Total n = 95; Int Grp1 n = 43; Int Grp2 n = 16; Int Grp3 n = 16; Cntrl n = 20 Setting: varied by treatment arm Mean age (SD): Total: 46.8y (11.5); IntGrp1: 44.7 y(12.7); IntGrp2: 48.5 y(10.6); IntGrp3: 50.0 y (12.6); Cntrl: 47.3 y (7.9) Gender: Total: 48.4% male; IntGrp1: 44.2% male; IntGrp2: 58.8% male; IntGrp3: 46.7% male; Cntrl: 50% male</p> <p>Presumed etiology: Idiopathic, exclude Moribus Meniere Duration of tinnitus: NR Severity: Subjective annoyance >40 on 9 scales assessing disruptiveness of tinnitus Number of dropouts: Int Grp1 n = 13; Int Grp2 n = 4; Int Grp3 n = 4; Cntrl n = 0 Reasons for dropouts: NR Comorbidities: NR</p>	<p>CBT Tinnitus Coping Therapy (TCT); Education; Relaxation Therapy Int Grp1: TCT= detailed training manual provided guidelines for 11 sessions Int Grp2: Minimal Contact-Education (MC-E) comprised 2 education sessions regarding tinnitus etiology, 4 weeks self-help exercise Int Grp3: Minimal Contact-Relaxation (MC-R) 4 sessions; educational, verbal relaxation; discussions</p> <p>Comparator: Wait-list Cntrl Duration of treatment: Int Grp1: 11 sessions 90-120 minutes; Int Grp2: 2 sessions (4 weeks); Int Grp3: 4 sessions</p> <p>Number of followups: Int Grp1: 3 followups (immediately post-treatment 6 and 12 months after treatment); Int Grp2 and Int Grp3: 1 followup (immediately post-treatment)</p> <p>Duration of study: NR</p>	<p>Depression (ADS) G-QOL (SCL-90R) TS-QOL (TDI, TQ*, TC cope subscales) Loudness (Diary)</p>	<p>TSQOL: WLC group ($F(1,34)=6.79$, $p < 0.01$) on the TEI; TQ=NS</p> <p>There is no significant superiority of TCT relative to the combined MC treatments in subjective change.</p> <p>Concluded that the CBT outpatient group training of tinnitus shows good efficacy in reducing the negative impact of tinnitus on the person's life by improving coping and reducing the threatening character of tinnitus.</p> <p>Adverse Events: NR</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Malouff, ⁹⁵ 2010 Australia	<p>Baseline sample: Total n = 162 Interven n = 84; Cntrl n = 78 Setting: Internet online participation Mean age (SD): Interven 1: 57.3y (13.7); Cntrl: 57.8y (13.3) Gender: Interven: 51% male; Cntrl: 60.3% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: NR Severity of tinnitus: NR Number of dropouts n = 35; Interven: n = 29 (35%); Cntrl n = 8 (10%) Reasons for dropouts: NR Audiological factors: NR Comorbidities: NR</p>	<p>Participants received a book based on cognitive-behavioral principles, including educational information on tinnitus, cognitive reappraisal and restructuring, relaxation and stress management techniques, attention Cntrl techniques, use of self-instruction, making lifestyle changes, and maintaining gains. A brief letter asking participants to read the book and to follow the suggestions it contained in the subsequent 6 weeks.</p> <p>Comparator: WLC</p> <p>Duration of Treatment: 2 months Number of followups: 2m, 4m, 12m Duration of study: NR</p>	<p>G-QOL (GPQ-12)</p> <p>TS-QOL (TRQ)</p>	<p>Individuals in the Interven condition who completed the post-assessment experienced a significant reduction in tinnitus distress from pre-Interven to post-Interven (p =.0001]. The between-groups difference in the rates of reliable change, although in the hypothesized direction, was not statistically significant (p =.15).</p> <p>Intention-to-treat analyses showed no significant effect for between-groups analyses, but did show a significant effect for the 1-year follow-up pre-post analysis.</p> <p>Adverse Events: None</p>
Rief, ¹⁰⁴ 2005 Germany	<p>Baseline sample: Total n= 42 Interven n = 22; Cntrl n = 20 Setting: University psychotherapy outpatient clinic Mean age (SD): Interven: 45.5y (12.8); Cntrl: 48.0y (15.3) Gender: Interven: 59.1% male; Cntrl: 40.0% male</p> <p>Presumed etiology of tinnitus: NR Duration of tinnitus: Interven: 4.5 y (5.3); Cntrl: 8.3 y (7.7) Severity of tinnitus: (VAS out of 10) Interven: 6.5 (1.7); Cntrl: 5.9 (1.6) Number of dropouts: 1 Interven n = 0; Cntrl n = 1 Reasons for dropouts: discontinued Interven Audiological factors: hearing problems (57%) Comorbidities: depressive disorder: 36.4% 1st Interven group; 35.0% wait list group</p>	<p>CBT Training consisted of 1 pre-assessment session, 7 treatment sessions, and a final session summarizing Interven strategies and conducting post-assessment. Training was manual-guided, included handouts (basic information on ear and the hearing system; information processes involved in tinnitus; the vicious circle of tinnitus annoyance, muscular reactivity, and selective attention; and aspects of tinnitus maintenance, modulating factors, etc.).</p> <p>Comparator: Waiting-list Cntrl Setting: outpatient clinic Duration of Treatment: 8 weeks Number of followups: 1 (6 months) Duration of study: October 2002 to November 2003</p>	<p>TS-QOL (TQ)</p> <p>G-QOL (HRLS*, GSI, SCL-90R)</p> <p>Loudness (diary)</p>	<p>On most tinnitus specific variables, patients in the treatment group improved significantly more than patients on the Wait List Cntrl.</p> <p>Main effect sizes for tinnitus-specific variables were up to 0.89.</p> <p>Adverse events: Participants did not report any adverse events</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Scott, ⁷ 1985 Sweden	<p>Baseline sample: Total n=24; Interven=12; Cntrl=12 Setting: Department of Audiology, Hospital Mean age: 52.6 Interven: 50.9 y; Cntrl: 54.3 y Gender: Total: 43.4% male Interven: 41.6% male; Cntrl: 45.5% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: mean 9.4y (1-23 years) Severity of tinnitus: grade 2 or 3 (Klockhoff & Lindblom) Number of dropouts: 2 Cntrl group, women Reasons for dropouts: NR Audiological factors: All had some form of hearing impairment Comorbidities: no retrocochlear lesions suspected</p>	<p>Relaxation Therapy vs wait list The treatment comprised 10 one-hour sessions over 3 weeks: relaxation training, training of self-control by distraction exercises with the aim of reducing the discomfort from tinnitus, and application of the method in situations associated with tinnitus.</p> <p>Comparator: WLC</p> <p>Duration of treatment; 10 to 11 weeks Number of follow ups: 1 Duration of study: NR</p>	<p>Depression (Self-report R)</p> <p>TS-QOL (Self-report D)</p> <p>Loudness (Self-report D)</p>	<p>TS-QOL: A significant effect on both direct (group x time interaction: $F(1,21)=6.01$, $p < 0.05$) and retrospective measures (group x time interaction: $F(1,21)=7.92$, $p < 0.01$)</p> <p>Adverse Events: 8 (38%) reported an increase of negative effects of the intensive self-monitoring on the loudness of and discomfort from their tinnitus. 14/15 patients reported a general reduction of dizziness, headache and troublesome muscle tension.</p>
Weise, ¹⁴ 2008 Germany	<p>Baseline sample: Total n = 111 Setting: Outpatient treatment center for psychological Intervens Mean age (SD): Interven: 49.5 y (11.83); Cntrl: 52.9 y (11.92) Gender: Interven: 55.8% male Cntrl: 55.9% male</p> <p>Presumed etiology: Idiopathic Duration of tinnitus: >6 months Severity of tinnitus: High tinnitus annoyance Number of dropouts: Interven n = 15; Cntrl n = 20 Reasons for dropouts: Interven: incomplete (4), discontinued Interven (7), refused follow-up assessment (4); Cntrl=1 incomplete (1), discontinued waiting period (7), discontinued Interven (7), refused follow-up assessment (5) Comorbidities: Depression</p>	<p>Biofeedback-based CBT</p> <p>Interven: 12 sessions of 20 mins. of biofeedback training combined with 20 mins of CBT. Treatment over 3 months.</p> <p>Comparator: Waitlist group measured at initiation, 3 months later, then had the Interven and measured again after Interven (6 months).</p> <p>Duration of treatment: 3 months Number of follow ups: 1 (6 months) Duration of study: 9 months</p>	<p>Loudness (VAS)</p> <p>Sleep (VAS*, TQ-sub)</p> <p>G-QOL (GSI SCL-90-R)</p> <p>Depression (BDI)</p> <p>TS-QOL (TQ*, VAS, TRSS catastrophizing, TRCS helplessness)</p>	<p>For the TQ and the tinnitus diary, the MANOVA showed a statistically significant group effect, $F(13, 97) = 2.84$, $p < .01$; a significant time effect, $F(13, 97) = 14.75$, $p < .001$; and a significant interaction for Time x Group, $F(13, 97) = 5.16$, $p < .001$ for the completer analysis.</p> <p>Improvements were maintained over a 6-month follow-up period in which medium-to-large effect sizes were observed.</p> <p>Adverse Events: Majority of the patients did not experience negative side effects caused by the treatment</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Westin, ¹¹² , 2011 Sweden	<p>Baseline sample: n = 64 Interven1 (ACT): n = 22; Cntrl (WLC): n = 22; Interven2 (TRT): n = 20 Setting: Audiology department Mean age (SD): Interven1: 53.5 years (12.84) Cntrl: 49.59 years (11.86) Interven2: 48.95 (14.3) Gender: 53.1% male</p> <p>Presumed etiology of tinnitus: Idiopathic Duration of tinnitus: Mean 8.3 y (SD 7.3) Severity of tinnitus: score \geq30 on THI Number of dropouts: 4 Reasons for dropouts: NR Audiological factors: 12.8 dB hearing level (SD=7.1) for better ear Comorbidities: n=49: rheumatological conditions (n=35), cardiovascular conditions (n=10), respiratory conditions or allergy (n=10), mild to moderate depression (n=9), gastroenterological conditions (n=6), sleep problems (n=6), cancer (n=5), endocrinological conditions (n=6), skin disease (n=2).</p>	<p>CBT Acceptance and Commitment Therapy (ACT)</p> <p>ACT: max 10 weekly individual sessions of 60 minutes TRT: one 2.5 hr individual consultation session, 30 min follow-up session over telephone, wearable sound generators used min 8 hrs/day for 18 months WLC started CBT treatment after 10 weeks</p> <p>Duration of treatment: 10 weeks to 18 months Number of follow ups: 3 Duration of study: 18 months</p>	<p>Sleep (ISI)</p> <p>TS-QOL (THI)</p> <p>Anxiety (HADS-A)</p> <p>Depression (HADS-D)</p> <p>G-QOL (QOLI)</p>	<p>A comparison between the active treatments, including all assessment points, revealed significant differences in favor of ACT regarding tinnitus impact (Cohen's d = 0.75) and problems with sleep.</p> <p>No significant main effects were found. On QOL, anxiety or depression no time, group or interaction effects were found.</p> <p>.Adverse Events: None</p>

Table E4. Psychological/behavioral intervention and outcomes (n=19) (continued)

Author Year Setting	Population Description	Intervention	Outcome Measures	Results
Zachriat, ¹¹³ 2004 Germany	<p>Baseline sample: Total n = 77 TCT n = 27; HT n = 30 EDU n = 20 Setting: University Psychology department Mean age (SD): TCT: 53.8y (11.8); HT: 51.6y (11.0); EDU: 56.1y(10.6) Gender: TCT: 59.3% male; HT: 66.7% male; EDU: 74.0% male</p> <p>Presumed etiology of tinnitus: idiopathic Duration of tinnitus: ≥3 months (range 4 to 324 m) Severity of tinnitus: TQ ≥ 25 Number of dropouts: TCT n = 2; HCT n = 1; EDU n = 3 Reasons for dropouts: NR Audiological factors: NR Comorbidities: no treatable organic disease</p>	<p>HT: Habituation-based treatment, 5 sessions – counseling concentrating on education of factors having an impact on tinnitus and training in sound generator use for ≥6 hours per day TCT: tinnitus coping training, 11 sessions, 90 to 120 minutes in groups of 6 to 8 – relaxation exercises, use of attention distraction strategies; coping techniques EDU: (Cntrl): educational interven, 1 session informing about physiology and psychology of tinnitus</p> <p>Duration of treatment: 15 weeks Number of followups: 3 to 27 weeks, 53 weeks, 18 to 21 months Duration of study: NR</p>	<p>G-QOL (VEV) TS-QOL (TQ, TCQ, JQ, Diary) Loudness (Diary)</p>	<p>Findings reveal highly significant improvements in both tinnitus coping training and habituation-based treatment in comparison with the Cntrl group.</p> <p>While tinnitus coping training and habituation-based treatment do not differ significantly in reduction of tinnitus disability, improvement in general well-being and adaptive behavior is greater in tinnitus coping training than habituation-based treatment.</p> <p>Adverse events: NR</p>

*Indicates the test used to measure outcomes which were selected to represent the domain in the forest plots (and subsequent SOE decisions)

Abbreviations: A/E = Adverse events; AMT = active motor threshold; Bef-Skala = Befindlichkeits-Skala; Bes-Liste = Beschwerden-Liste; CBT = cognitive behavioral treatment; Ctrl = Control; Dep-Skala = Depressivitäts-Skala; ENT = ear, nose and throat; grp = group; G-QOL = global quality of life; HADS = Hospital Anxiety and Depression Scale; interven = Intervention; month = month; ISI = Insomnia Severity Index; N/A = not applicable; NR = not reported; OSI-R = Occupational Stress Inventory- Revised; QOL = quality of life; RCT = randomized controlled trial; SD = standard deviation; TCT = Tinnitus Coping Therapy; THI = Tinnitus Handicap Inventory; TMJ = temporal mandibular joint; TRCS = Tinnitus-Related Control Scale; TRSS = Tinnitus-related Self-Statements Scale; TS = tinnitus specific; TSQ = Tinnitus Severity Questionnaire; VAS = visual analog scale; week = week; WLC = wait list Cntrl; yr = year

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Appendix F. List of Ongoing Clinical Trials Evaluating Interventions To Treat Idiopathic Tinnitus Registered in Clinicaltrials.gov

Table F1. Ongoing clinical trials evaluating medical surgical interventions

Med/Surg Intervention Category	Study Title (NCT number)	Intervention	Sponsor Completion date
<i>Psychoactive (Neurotransmitter) drugs</i>	A Study on the Effect of Cilostazol in Patients With Chronic Tinnitus (NCT01378650)	Drug: Cilostazol; Drug: Placebo	Asan Medical Center; Jong Woo Chung; Korea Otsuka Pharmaceutical Co.,Ltd December 2011; this study is currently recruiting participants
<i>Other drugs</i>	Safety Study for NST-001 and the Neuroject Injection Set to Treat Tinnitus (NCT00957788)	Drug: NST-001	NeuroSystem Corporation December 2011; this study is currently recruiting participants
	Comparison of Single Versus Repeat Doses of AM-101 in the Treatment of Acute Inner Ear Tinnitus (NCT01270282)	Drug: AM-101	Auris Medical, Inc. February 2013
<i>Other</i>	Investigating the Neurobiology of Tinnitus (NCT01294124)	No Intervention: Prospective study	Washington University School of Medicine; Department of Defense May 2014
	A Trial of Magnesium Dependent Tinnitus (NCT01273883)	Dietary Supplement: Magnesium; Other: Placebo	Mayo Clinic July 2013

Abbreviations: med/surg = medical/surgical; NCT = National Clinical Trial

Table F2. Ongoing clinical trials evaluating medical surgical interventions using rTMS or vagal nerve stimulation

Med/Surg Intervention Category	Study Title (NCT number)	Intervention	Sponsor Completion date
Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - ACTIVE; Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - SHAM	Effect of rTMS on Resting State Brain Activity in Tinnitus (NCT00926237)	Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - ACTIVE; Device: Repetitive Transcranial Magnetic Stimulation (rTMS) - SHAM	University of Arkansas; National Institutes of Health (NIH) March 2016
Device: repetitive transcranial magnetic stimulation (rTMS); Device: placebo rTMS	Transcranial Magnetic Stimulation for Tinnitus (NCT01104207)	Device: repetitive transcranial magnetic stimulation (rTMS); Device: placebo rTMS	Department of Veterans Affairs December 2014
Device: Bimodal Repetitive Transcranial Magnetic Stimulation	rTMS Bimodal Treatment For Tinnitus: A Pilot Study (NCT01590264)	Device: Bimodal Repetitive Transcranial Magnetic Stimulation	Washington University School of Medicine November 2012
Device: Repetitive Transcranial Magnetic Stimulation (rTMS)	Repetitive Transcranial Magnetic Stimulation for Tinnitus Treatment (NCT01093872)	Device: Repetitive Transcranial Magnetic Stimulation (rTMS)	Singapore General Hospital August 2013
Device: tVNS-Device	The Treatment of Tinnitus With Transcutaneous Non-invasive Vagus Nerve Stimulation (NCT01176734)	Device: tVNS-Device	cerbomed GmbH July 2012
Device: vagus nerve stimulation (VNS)			
Device: rTMS	Repetitive Transcranial Magnetic Stimulation With Double Cone Coil in Chronic Tinnitus (Ti-CDC) (NCT01663311)	Device: Medial Frontal rTMS Double-Cone-Coil; Device: Left DLPFC Butterfly Coil	University of Regensburg December 2013
Device: Low frequency rTMS	rTMS for the Treatment of Chronic Tinnitus: Optimization by Simulation of the Cortical Tinnitus Network (Triple) (NCT01663324)	Device: Magventure Mag Pro Option	University of Regensburg March 2014

Table F3. Ongoing clinical trials evaluating psychological/behavioral interventions

Psych/Beh Intervention	Study Title (NCT number)	Intervention	Sponsor Completion date
<i>CBT/CBT combination</i>	Cognitive Behavioral Therapy (CBT) for Tinnitus (NCT00724152)	CBT/Education Training/Usual Care	Department of Veterans Affairs; Yale University January 2013
	Treatment of Chronic Bothersome Tinnitus Using Cognitive Training and D-cycloserine (NCT01550796)	Behavioral: Cognitive Training; Drug: placebo	Washington University School of Medicine June 2012
<i>Other psych/behavioral</i>	Cognitive Training for Firefighters With Tinnitus (NCT01458821)	Brain Fitness Program - Tinnitus	Washington University School of Medicine; Federal Emergency Management Agency October 2013
	Mindfulness Based Tinnitus Reduction (MBTR): A Symptom Perception Shift Program (NCT01229709)	Mindfulness Based Tinnitus Reduction/Treatment as Usual	University of California, San Francisco January 2015
	Multi-Site Evaluation of Progressive Tinnitus Management (NCT01015781)	Progressive Tinnitus Management/Treatment as Usual	Department of Veterans Affairs June 2013
	Telephone Tinnitus Education for Patients With Traumatic Brain Injury (TBI) (NCT01129141)	Telephone Tinnitus Education/Wait List Control	Department of Veterans Affairs September 2014
	Neuro-Music Therapy for Recent Onset Tinnitus: Evaluation of a Therapy Concept (NCT01566708)	Neuro-Music Therapy immediately/after waiting time/Music-therapeutical stress management coaching	German Center for Music Therapy Research; University Hospital for Ear, Nose, and Throat, University of Heidelberg, Germany; Clinic of Diagnostic and Interventional Neuroradiology, Saarland University Clinic, Homburg, Germany July 2013
	New Therapy for Patients With Severe Tinnitus (NCT01480193)	Other: Sound Based and Educational (SBE) Therapies; Other: Integrated Medicine Therapies and Sound Based Education Therapies; Other: Integrated Medicine Therapies and SBE	Duke University; National Institutes of Health (NIH); National Institute on Deafness and Other Communication Disorders (NIDCD) October 2013

Abbreviations: CBT = cognitive behavioural therapy

Table F4. Ongoing clinical trials evaluating sensory modulation or other devices

Devices Category	Study Title (NCT number)	Intervention	Sponsor Completion date
Coventional/ Placebo Sound Generator	Tinnitus Retraining Therapy Trial (NCT01177137)	Coventional/Placebo Sound Generator (SG)	Johns Hopkins Bloomberg School of Public Health; National Institute on Deafness and Other Communication Disorders (NIDCD); University of Alabama, Tuscaloosa; David Grant U.S. Air Force Medical Center; Wilford Hall Medical Center; United States Naval Medical Center, San Diego; United States Naval Medical Center, Portsmouth; National Naval Medical Center; Naval Hospital Camp Pendleton February 2015
Device: CR Neuromodulation	Evaluation of the CR Neuromodulation Treatment for Tinnitus (NCT01541969)	Device: CR Neuromodulation	Nottingham University Hospitals NHS Trust; University of Nottingham; University College, London November 2013
Device: BrainSTIM Transcranial Stimulator	Transcranial Direct Current Stimulation (tDCS) for the Treatment of Tinnitus (NCT01575496)	Device: BrainSTIM Transcranial Stimulator	Centre Hospitalier Universitaire Vaudois January 2015
The Inhibitor™ Tinnitus Masking Device	Inhibitor Masking Device & SCN9 Gene Expression (NCT01412918)	The Inhibitor™ Tinnitus Masking Device	Medical College of Wisconsin December 2016
Device: P-Stim	Somatosensory Based Treatments for Tinnitus (NCT01066273)	Device: P-Stim	Massachusetts Eye and Ear Infirmary December 2015 - Withdrawn
Device: ANM T30 CR®- System	Acoustic Coordinated Reset (CR®) Neuromodulation for the Treatment of Chronic Tonal Tinnitus (“RESET Real Life”) (NCT01435317)	Device: ANM T30 CR®- System	ANM Adaptive Neuromodulation GmbH; Ceres GmbH evaluation & research July 2013
Device: Customized sound; Regular masker	Customized Acoustic Stimulation for the Treatment of Tinnitus (NCT01487447)	Device: Customized sound; Device: Regular masker	University of California, Irvine July 2012: this study is still recruiting participants
Device: Smartphone and web based TRT	Efficacy of Internet and Smartphone Application- delivered Tinnitus Retraining Therapy (NCT01663467)	Device: modified TRT using smartphone and web based materials; Drug: Gingko biloba	Seoul National University Hospital; Soonchunhyang University Hospital December 2013

Abbreviations: PSTIM = pulse stimulation treatment; TRT = Tinnitus Retraining Therapy