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Evaluation and Treatment of Tinnitus: A Comparative Effectiveness Review

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The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

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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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

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We welcome comments on this CER. 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 e-mail to epc@ahrq.hhs.gov.

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Evaluation and Treatment of Tinnitus: A Comparative Effectiveness Review

Structured Abstract

Objectives: A review was undertaken to evaluate several areas of managing idiopathic tinnitus and these included:(1) measures used to assess patients for subsequent management (KQ1), (2) effectiveness of treatments (KQ2), and, (3) identification of prognostic factors (KQ3).

Data Sources: MEDLINE®, EMBASE®, CINAHL®, PsychINFO, AMED, Cochrane Database of Systematic Reviews, and Cochrane Central® were searched from January 1970 to June 2012. An extensive grey literature search was also undertaken including documents from regulatory and tinnitus-related organizations.

Review Methods: Standardized **s**ystematic review methodology was employed. Eligibility criteria included English studies of adults with subjective idiopathic (nonpulsatile) tinnitus and excluded studies where tinnitus was the result of middle ear pathologies or focused on methods determining malingering tinnitus. For KQ2, all pharmacological/ food supplements, medical, surgical, sound /technological, and psychological or behavioral interventions aimed at ameliorating tinnitus symptoms were eligible (except tapedectomy or tympanoplasty). RCTs with inactive controls or head to head trials were eligible for KQ2; there were no study design restrictions for KQ1 and KQ3.

Results: From 9,725 citations, there were 52 eligible publications that were extracted for data. None were eligible for KQ1 or KQ3. From the 52 publications eligible for KQ2, 17 evaluated pharmacological interventions, five sound technologies, 11 medical interventions (low level laser, acupuncture, transcranial magnetic stimulation), and 19 publications evaluating psycholocal/behavioral interventions. Adverse effects were generally poorly collected and reported across all interventions.

Conclusions: There is moderate strength of evidence (SOE) indicating that CBT interventions relative to inactive controls improve tinnitus-specific quality of life (QoL), and does not affect perceived loudness. There is low SOE that all pharmacological interventions improve tinnitus-specific QoL; there is low SOE that antidepressants improve anxiety and depression symptoms relative to placebo. There is insufficient SOE that any medical intervention evaluated improves tinnitus-specific QoL, perceived loudness, or anxiety and depression symptoms relative to inactive controls. The SOE for the adverse effect of sedation was judged insufficient. Future research should address the significant gaps identified for KQ1 and KQ3, and improve collection of adverse events, sample size, and dose specifications for interventions in KQ2.

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Executive Summary

Background

Tinnitus is the perception of sound in the absence of an external auditory stimulus and as such tinnitus is a symptom and not a disease. It can disturb one's day-to-day life in a number of ways including causing distress and annoyance, disruption of sleep, anxiety, and depression. An estimated 16 percent of the American population (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.[1] The prevalence of tinnitus increases with age and noise exposure.[2] 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 the 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. The severity of tinnitus experienced by patients may vary with or depend on comorbidities that can include mental health illnesses such as depression and anxiety.

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 defined as tinnitus that is perceptible by both patient and examiner. Subjective tinnitus is idiopathic and perceptible only by the patient. Due to the rarity of objective tinnitus, some investigators have argued that all tinnitus is subjective and should instead be classified by origin, either as somatic or neurophysiologic.[3] In this review, we will use the term *subjective idiopathic tinnitus* rather than neurophysiologic tinnitus because it is the term more commonly used in the literature at this time to describe the same condition, and is the most commonly diagnosed type of tinnitus.[4]

For cases of subjective idiopathic tinnitus in which tinnitus-specific intervention is indicated, the range of interventions can include, but is not limited to, medical/surgical treatments, sound treatments/technologies, and psychological/behavioral treatments as outlined below. It is also possible that multiple treatments are provided in combination or in a progressive approach depending on the needs of the patient. Medical surgical treatments can include (1) pharmacological interventions (there are no drugs with a specific indication for tinnitus, but antidepressants, anxiolytics, psychoactive neurotransmitters, vasodilators and vasoactive substances, and intravenous lidocaine have been used), (2) treatment for temporomandibular joint (TMJ) disease[5]as tinnitus is a key symptom in this problem (treatment of TMJ disease can range from the use of dental orthotics and self-care instructions to surgery[6]), (3) transcranial magnetic stimulation (TMS), and (4) complementary and alternative medicine therapies (CAM; including Gingko biloba extracts, acupuncture, and hyperbaric oxygen). Sound treatments and technologies can include (1) hearing aids, (2) cochlear implants, (3) tinnitus masking (sound generators) also known as sound-based relief, (4) Neuromonics Tinnitus Treatment,[7]and (5) tinnitus retraining therapy (TRT; a combination of acoustic stimulation with a structured program of counseling and support by a specially trained clinician). Psychological/behavioral treatments can include (1) biofeedback, (2) relaxation, (3) cognitive behavioral therapy (CBT), (4) psychotherapy, and (5) coping training.

Scope and Key Questions

In a rehabilitative context, the distress from tinnitus is often more common than hearing loss in triggering people to seek healthcare for their hearing, yet typical audiological interventions focus on the remediation of hearing loss rather than on treating tinnitus.[8] Recent research findings from cognitive and auditory neuroscience studies have advanced the 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.

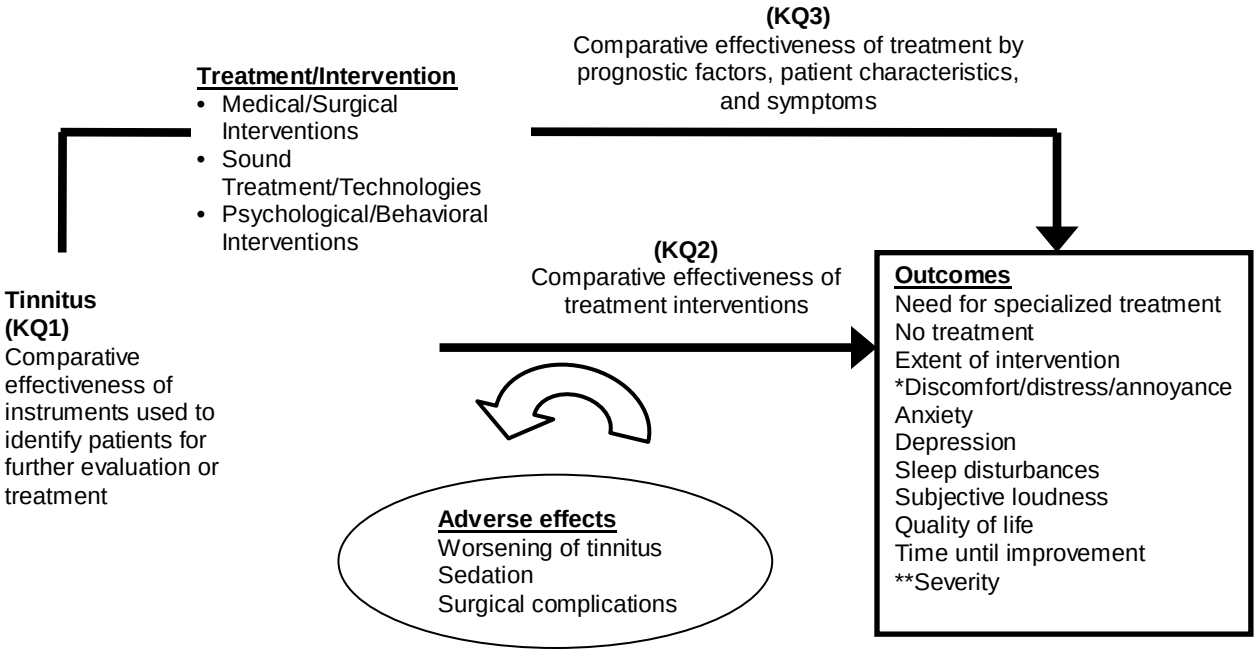
In 2008, the Tinnitus Research Initiative (TRI) created, and still continues to modify, a flowchart outlining steps for the diagnosis and management of tinnitus; however, this clinical protocol has yet to be adopted by any government or agency because the evidentiary base has not yet been evaluated.[9] The usability of the TRI flowchart is limited as it reflects a biomedical approach: an approach that would be used by physicians rather than by providers who implement behavioral methods. Organizations such as the American Tinnitus Association (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*[10]for the commissioning of tinnitus services and for managing tinnitus from primary care to specialist care.[11]The TRI flowchart and the U.K. 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 literature.[4,12] 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 systematic review aims to explore prognostic factors and strategies for the optimal management of tinnitus and to clarify the effectiveness and measurable outcomes of the various tinnitus treatments currently in use. This review also identifies gaps in the existing literature that will inform directions for future research. The key questions (KQs) are as follows:

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?

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?

Figure ES-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 33 studies, 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® from January 1970 to June 2012.The search strategy used medical subject headings (MeSH®), keywords, and text words including tinnitus, humans not animals, and limiting the search to English language citations. Grey literature sources were searched and these included regulatory agency websites (FDA, Health Canada, and the European Medicines Agency), clinical trial databases (clinicaltrials.gov, clinicaltrialsregister.eu, metaRegister of Current Controlled Trials, Trial Registries, Clinical Study Results, and WHO Clinical Trials), and conference sources (Conference Papers Index for the last 2 years only). In addition, the websites of the following tinnitus-related organizations were searched: 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. The Scientific Resource Center also requested the Scientific Information Packages for drugs and devices. In addition to the electronic database search, review of reference lists of eligible studies at full text screening was undertaken.

Criteria for Inclusion/Exclusion of Studies in the Review

Eligibility criteria are summarized below in Table ES-1. Based on input from the Technical Expert Panel (TEP), non-English-language publications were excluded.[13,14] Randomized controlled trials (RCTs) or observational studies with true control groups (e.g., cohort, case

control) were included when they provided details about methods and results to enable use of the data and results. Meta-analyses and systematic and narrative reviews were excluded, but reference lists were evaluated for potentially relevant citations (Table ES-1). At the full text screening level, articles were excluded for any of the previously cited reasons. For KQ2 and KQ3, studies were also excluded if there was not an intervention used to treat tinnitus (e.g., prevalence studies, studies to determine effects of tinnitus on brain wave patterns or memory); if tinnitus was the result of middle-ear pathologies (e.g., mechanics, otitis media, otosclerosis, etc.) or the intervention was a stapedectomy or tympanoplasty; and/or, if they were only focused on ways of determining whether a patient has malingering tinnitus.

Table ES-1. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	**KQ1:** Adult (≥18yrs) patients who visit healthcare practitioners with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds, etc.) **KQs 2 & 3:** Adults (≥18yrs) with a diagnosis of subjective idiopathic (nonpulsatile) tinnitus who are sufficiently bothered by tinnitus that they are seeking a treatment intervention	• Subjects <18 years of age • Dx of pulsatile tinnitus • Unilateral cases with specific medical Dx (e.g., pulsatile tinnitus with acoustic neuroma) • Tinnitus as side effect of drugs • Nonhuman
Interventions	**KQ1:**Direct observation or observation of sound with stethoscope; referral to a health professional with expertise on managing tinnitus (i.e., otolaryngologist, audiologist, neurologist, mental health professional); administration of scales/questionnaires to assess severity (e.g., THI, TRQ, TFI, VAS, etc.) **KQ2:** Any treatment/therapy used to reduce/help cope with tinnitus including but not limited to: **Medical/Surgical** • Pharmacological treatments (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: Gingko biloba extracts; acupuncture; hyperbaric oxygen therapy; diet, lifestyle, and sleep modifications (caffeine avoidance, exercise) **Sound Treatments/Technologies** • Hearing aids, cochlear implants, sound generators/maskers • Neuromonics, Tinnitus Retraining Therapy **Psychological/Behavioral** • Cognitive behavioral therapy, biofeedback, education, relaxation therapies, Progressive Tinnitus Management **Combination Therapies** • Any combination of tinnitus interventions (e.g., pharmacological treatment with cognitive behavioral therapy) **KQ3:** Any treatment/therapy used to reduce/help/cope with tinnitus including but not limited to those described in KQ2.	**KQ1:** Non direct observations **KQ2:** No exclusions for interventions **KQ3:** No exclusions for interventions

Table ES-1. Inclusion and exclusion criteria (cont'd)

Comparators	**KQ1:** Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus **KQ2:** Placebo; no treatment; wait list; treatment as usual; other intervention/treatment with control **KQ3:** • 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.	**KQ1:** No exclusions **KQ2:** No comparator/control **KQ3:** No exclusions
Outcomes	**KQ1:** Final outcome: No treatment; need for specialized treatment (e.g., audiology, otolaryngology, neurology, mental health care); extent of intervention **KQ2:** Sleep disturbance, discomfort, anxiety symptoms, depression symptoms, subjective loudness, quality of life, tinnitus severity, adverse effects (worsening of tinnitus, sedation, surgical complications) **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)	No exclusions
Publication languages	English	Non-English
Study design	**All KQs:** RCTs or observational studies with true control groups (e.g., cohort studies, case-control studies) **All KQs:** Original research studies must provide sufficient detail about methods and results to enable use and aggregation of the data and results **All KQs:** Relevant outcomes must be able to be extracted from data in the papers Controlled experimental studies (manipulation of treatment)	• Systematic reviews and narrative reviews (excluded but pulled for full reference list review), case reports/studies, and case series • Editorials, comments, letters, opinion pieces, and abstracts and webcasts.
Setting	Primary care; specialty care (audiology, otolaryngology, neurology, mental health); university research; internet	
Other criteria	Studies must address one 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) **All KQs:** Treatment approaches for adults at risk for a tinnitus diagnosis	

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 analogue scale; yrs = years

Data Extraction, Assessment of Risk of Bias, and Applicability

The Evidence-based Practice Center (EPC) staff members and clinical experts conducting this review jointly developed the data extraction forms and the evidence tables. Standardized and validated scales were used (the Newcastle-Ottawa quality assessment scales for case-control studies and cohort studies,[15] and the Jadad scale for RCTs[16]) to assess risk of bias; two raters evaluated the studies and consensus was reached to resolve disagreements. Applicability was assessed in accordance with Agency for Health Research and Quality (AHRQ) recommendations.[17]The basis for applicability assessment of our findings was limited to the populations, interventions, outcomes, and settings described in the protocol, such that they would apply to the whole idiopathic tinnitus population seeking treatment in typical centers of care.

Data Synthesis and Rating the Strength of Evidence

All included studies have been summarized in narrative form and presented for each KQ and stratified by the different outcomes and interventions. Meta-analysis was not undertaken due to the clinical heterogeneity of the interventions and outcomes; we estimated the standardized mean differences for each study and showed these in forest plots to compare effect sizes across studies.

Two reviewers assessed the overall strength of evidence (SOE) for each KQ using the AHRQ standards for evaluating intervention studies, which is based on methods developed by the GRADE Working Group.[18,19] Several domains of quality were considered in the final evaluation and these included, risk of bias, consistency of results (concerns homogeneity in direction and magnitude of results across different studies), 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), and precision (refers to the width of confidence intervals for diagnostic accuracy outcomes, and the effect size for treatment monitoring; this domain is related to study sample size). Other key domains (publication bias, dose-response association, existence of plausible unmeasured confounders, and strength of association) were considered The strength of evidence was classified into four grades based on the AHRQ EPC Program approach: high, moderate, low, or insufficient.[18,19] We assessed the SOE for the six outcomes of benefit (tinnitus related quality of life, perceived loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global quality of life) and outcomes of harm (sedation only).

Results

The initial search yielded 9,725 unique citations. At title and abstract screening, 8,891 articles were excluded and 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 and 21 were not eligible for extraction. All studies were eligible for KQ2.

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 eligible studies were found for this key question.

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 intervention (including combinations of interventions)?

Characteristics of the Included Studies

Seventy three studies passed through full text screening. From these 51 studies (52 included publications)[20-71] had sufficient data for extraction and addressed KQ2. An additional 21studies met eligibility criteria but were not extracted or presented in this CER because they did not report measures of variance for study outcomes[72-88] or presented results as proportions.[89-92]

We organized the eligible studies based on intervention groupings suggested by the Technical Expert Panel. Results are organized by type of intervention (i.e., pharmacological/food supplement; medical; sound technologies; and psychological and behavioral). Within each intervention section, the discussion of the data is then organized by the primary outcomes (tinnitus-specific quality of life (QoL), perceived loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global QoL).

Pharmacological or Food Supplement Interventions

A total of 17 articles[21,25,26,32,35,41,43,51,52,55,57,59,61,62,65,68,71] reported on 16 unique studies that evaluated interventions in the pharmacological or food supplement domain. Five articles[32,41,59,62,71] investigated antidepressant drugs versus placebo. These drugs included sertraline,[41,71] paroxetine,[59] trazodone,[32] and nortriptyline.[62] Five publications[21,43,55,61,68] examined psychoactive (neurotransmitter) drugs versus placebo. The psychoactive drugs were gabapentin,[55] baclofen,[68] alprazolam,[43] and acamprosate.[21,61] Three studies investigated other drugs, including methylprednisolone versus placebo,[65] vardenafil versus placebo,[51] and clonazepam plus Deanxit versus clonazepam plus placebo.[52] Four papers evaluated food supplements, with two[35,57] focused on Gingko biloba, one[26] on zinc, and one[25] on honeybee larvae. All food supplements were compared to placebo (which was hydrogenated dextrin in the larvae study). All of the studies were RCTs. The risk of bias, taken across all of the studies, was low to medium.

Tinnitus-Specific Quality of Life

Four studies (five publications)[21,41,52,62,71] assessed tinnitus-specific QoL by measuring discomfort, disturbance, or annoyance. Eleven studies (12 publications)[25,35,41,51,52,55,57,59,62,65,68,71] examined tinnitus-specific QoL by measuring severity. One study used both.[32]

For the most part, interventions failed to show improved tinnitus-specific QoL; statistically significant improvement was seen for acamprosate[21] (when measured as “disturbance”) and sertraline.[41,71] One study[62] found conflicting results for tinnitus-specific QoL (e.g., improved QoL or no difference compared to placebo) depending on the outcome measure.
Strength of evidence (SOE) was low, showing improvement in tinnitus-specific QoL in the case of each intervention group (antidepressants, psychoactive drugs, other, and food supplements) relative to a placebo comparator. Effect sizes were inconsistent regarding direction of effect; included studies, when taken together, had medium risk of bias.

Subjective loudness

Eight studies (nine publications)[26,35,41,43,52,61,65,68,71] examined loudness, primarily using subjective Visual Analog Scale (VAS) type scales. In two studies, active treatments—zinc[26,41,71] and sertraline[41,71]—had more impact on loudness than comparators. The SOE is insufficient for the antidepressant, other drug, and food supplement groups because only one study in each group could be used to make judgments about SOE. In the psychoactive drugs group, SOE is low, despite the fact that consistency across the results suggests benefits for these drugs compared to placebo. Risk of bias for the psychoactive drugs is medium, and effect estimates are imprecise due to small sample sizes, a lack of power calculations, and the heterogeneity of the interventions.

Sleep Disturbance

Three studies looked at the effect of paroxetine,[59] vardenafil,[51] and Deanxit[52] on the outcome of sleep disturbance. No statistically significant differences were found. The SOE is insufficient for sleep disturbance because only one study in each of the two relevant intervention groups could be used to make judgments about SOE. The Deanxit study[52] could not be used to assess SOE because the authors compared baseline scores to treatment order and did not evaluate the efficacy of the intervention relative to placebo.

Anxiety Symptoms

Three placebo-controlled studies examined the effect of sertraline (2 publications),[41,71] paroxetine,[59] and nortriptyline[62] on anxiety as an outcome. Statistically significant improvement in anxiety was seen for sertraline[41,71] but not the other interventions. The SOE is low for antidepressants decreasing anxiety symptoms relative to placebo. 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.

Depression Symptoms

Five studies (six publications)[25,41,52,59,62,71] considered depression as an outcome. In the nortriptyline study,[62] a statistically significant improvement was seen in the treated group. Sertraline also had a greater impact on reducing depressive symptoms,[41,71] although the reduction failed to reach statistical significance at the 5% level on one of the three scales used to measure depression. One study[25] of enzymolyzed honeybee larvae found one statistically significant difference favoring honeybee larvae in a subgroup analysis of one question (on depression) in an inventory of 25 questions.

The SOE is low for antidepressants[41,59,62,71] showing improvement of depression symptoms relative to the placebo comparator; the risk of bias was medium, 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 Deanxit[52] and honeybee larvae[25] because only one study evaluated each of these interventions.

Global Quality of Life

Six studies (seven publications) examined global QoL.[32,41,51,57,59,61,71] Sertraline was shown to be more efficacious than placebo in improving global QoL.[41,71] The SOE is low for antidepressants showing improvement in global QoL relative to placebo, because risk of bias was medium, 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

acamprosate,[61] vardenafil,[51] and Ginkgo biloba[57] because only one study evaluated each of these interventions.

Adverse Effects

Adverse effects spanned a range of clinical severity, from dry or sour mouth[32,59] to confusion,[68] but generally subsided after discontinuation of treatment. The study protocol identified surgical outcomes, sedation, and worsening symptoms as being the adverse effects of primary interest. Four studies[32,43,59,68] reported symptoms of sedation (sleepiness, drowsiness) during the use of antidepressants (trazadone and paroxetine) and psychoactive drugs (baclofen, alprazolam). 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.

Medical Interventions

Characteristics of Included Studies

Eleven studies were included for medical interventions in KQ2. Six[22,28,36,48,50,56] of these evaluated Repetitive Transcranial Magnetic Stimulation (rTMS) or electromagnetic stimulation, three evaluated low level laser therapy (LLLT),[30,53,64] and one each evaluated acupuncture[66] and acoustic coordinated reset neuromodulation (ACRN) therapy.[63] All the studies in the medical intervention grouping have relatively small sample sizes (less than 60 subjects total). The risk of bias in the eleven studies evaluating medical interventions was generally fair (n=9 fair,[22,30,36,48,50,53,63,64,66] n=1 poor,[28] n=1 good[56]).

Tinnitus-Specific Quality of Life

Four studies that evaluated rTMS[22,28,50,56] and one that evaluated electromagnetic stimulation[36] looked at the outcome of tinnitus-specific QoL. The direction of effect was inconsistent across studies; high frequency rTMS studies[28,56] showed differing directions of effect (statistically significant differences favoring treatment or no difference between groups), and low frequency rTMS studies[22,50] favored treatment but were not statistically significant. The magnitude of treatment effects also varied from 0.02 to -1.23. The small sample sizes, lack of power calculations, and wide confidence intervals contributed to our rating of imprecision. The SOE for rTMS for the outcome of tinnitus-specific QoL is rated as insufficient.

The single study evaluating Acoustic Coordinated Reset Neuromodulation (ACRN) interventions using several treatment groups did not show consistent statistically significant differences relative to placebo. We deemed the evidence as insufficient given the high risk of bias, small sample size, and high risk of publication bias.

Two studies at high risk of bias[53,64] evaluated LLLT compared to an inactive control, and one study[30] compared LLLT plus counseling to sham LLLT and counseling (also at high risk of bias). The studies showed no statistical differences between the treatment and comparator groups. The confidence intervals overlapped substantially, and the small sample sizes and lack of power calculations were factors that led to a rating of imprecision. Because of these factors and the fact that the types of laser were markedly different, the evidence for the LLLT versus sham LLLT studies was deemed insufficient.

A single trial[66] at high risk of bias compared traditional Chinese acupuncture to sham acupuncture and did not show a statistically significant benefit for acupuncture. We deemed the evidence as insufficient given the high risk of bias and small sample size.

Subjective loudness

Four studies with high risk of bias[28,53,63,64,66] examined loudness as an outcome in persons given medical interventions including LLLT and acupuncture. All the studies measuring this outcome consistently showed no statistical differences between treatment and inactive control groups; however, the studies had small sample sizes and it is not clear if this is a factor in the results, and as such, the studies are considered imprecise. SOE is rated as insufficient for all interventions compared to placebo.

Anxiety Symptoms

One study at high risk of bias[53] evaluated active versus sham LLLT. The LLLT group had a greater reduction than the control group in anxiety symptoms, but the difference was not statistically significant. The SOE for this single study was rated as insufficient.

Depression Symptoms

A single study at high risk of bias[53] evaluated depressive symptoms following the use of LLLT and found small non-significant difference favoring the active LLLT group. The SOE for this single study was rated as insufficient.

Sleep Disturbance

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

Global Quality of Life

None of the studies evaluating medical interventions measured the impact on global QoL.

Adverse Effects

Adverse effects (AE) were not consistently reported or specified in the methods of the studies. None of the studies in the medical interventions group reported drop-outs related to adverse effects. 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.

Sound Technology Interventions

Characteristics of Included Studies

Five publications (of four studies) were included.[31,33,34,40,54] All four studies[31,34,40,54] focused on head to head comparison including hearing aids versus sound generators;[54] one-stage intermittent perception plus two-stage complete covering of perception initially, then intermittent;[31] information only, information plus relaxation training, information plus long-term low level white noise (LTWN), and information plus relaxation training plus LTWN;[34] and cognitive behavior therapy (CBT) with noise generator (NG), CBT alone, tinnitus education (TE) plus NG, and TE with no NG.[40] The risk of bias in the four studies evaluating sound treatments/technology interventions was mixed (n=3 fair; n=1 poor).[31,34,40,54]

The types of sound technologies and comparator groups within each study were markedly diverse. All the studies evaluating sound technologies (relative to different active comparators) were considered to be at high risk of bias and consistency is unknown. Overall, there is insufficient information to judge the SOE for the head to head studies evaluating sound technologies.

Tinnitus-specific Quality of Life

All studies measured the effectiveness of treatment using a tinnitus-specific measure. Overall, significant benefits of treatment in terms of tinnitus-specific QoL 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 evaluated the effects of intervention on the subjective loudness of the tinnitus.[34,40,54] 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 disturbance.

Anxiety

Only one study[40] evaluated the effects of sound technology interventions on anxiety symptoms. All groups demonstrated improvement, but no statistically significant additional benefit due to NG was observed when it was combined with either TE or CBT.

Depression

Only one study reported the effects of the interventions on depression symptoms. No significant effect of CBT treatment either with or without NGs was found.

Global Quality of Life

Global QoL was measured in three studies.[34,40,54] Overall, although benefits of treatment were reported for tinnitus retraining therapy (TRT) using either sound generators or open ear hearing aids, no benefits were reported for the other interventions and no differences between treatments were discernible using this outcome.

Psychological and Behavioral Interventions

Characteristics of Included Studies

A total of 19 RCT articles[20,23,24,27,29,37-39,42,44-47,49,58,60,67,69,70] evaluated interventions in the psychological and behavioral domain. The risk of bias in these 19 RCTs was mixed (n=9 fair;[20,27,38,39,44,58,67,69,70] n=8 poor;[24,37,42,45-47,49,60] and, n=2 good).[23,29]

Tinnitus-specific Quality of Life

Fifteen RCT studies with waitlist controls investigated the effects of 27 interventions on tinnitus-specific measures related to QoL.[23,24,27,37-39,42,44,46,47,49,58,60,67,69] Studies of CBT interventions (8 RCTs) showed a benefit for improving tinnitus-specific QoL, with the direction of effect being rated as consistent with all but three studies showing statistically significant

differences. The SOE is moderate for CBT interventions improving tinnitus-specific QoL in studies with inactive controls.

For TRT therapies (2 RCTs[39,69]), both studies favored treatment but only one was significant. The SOE for TRT interventions for the outcome of tinnitus related QoL is rated as insufficient.

Three small RCTs evaluated the effect of relaxation therapy on tinnitus-specific QoL.[42,46,60] The studies were at high risk of bias and showed wide confidence intervals suggesting imprecision. All but one study favored relaxation therapy relative to inactive control, but only one study was statistically significant. The SOE for relaxation therapy is rated as insufficient.

Seven RCT studies evaluated the effect of seven other psychological and behavioral interventions on tinnitus-specific QoL.[27,37,44,46,47,49,69] Interventions included acceptance and commitment therapy,[69] Qigong (mindful exercise),[27] yoga,[47] a minimal educational intervention,[46] CBT combined with education,[37] bibliotherapy,[49] and a self-help book with telephone therapy.[44] Results in favor of treatment in comparison to an inactive control group were seen for educational counseling, self-help book with telephone therapy, and acceptance and commitment therapy (ACT). We deemed the evidence from these studies as insufficient given the high risk of bias and small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes of the study and the single studies within this group.

Subjective loudness

Eight RCT studies with waitlist controls investigated the effects of 16 interventions on the subjective loudness of tinnitus.[37,42,44,46,47,58,60,67] Six interventions in the CBT category were evaluated and a significant beneficial effect of biofeedback-based CBT[67] was reported. No significant effects of treatment on subjective loudness were reported for the other interventions in this category, including a CBT plus education intervention,[37] a CBT plus tinnitus coping training (TCT) intervention,[46] and a TCT intervention delivered by two different clinicians.[47] The SOE for CBT interventions for the outcome of loudness is rated as moderate; CBT interventions show improved perception of loudness relative to inactive comparators.

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.[42,46,60] The studies were at high risk of bias. 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 SOE for relaxation therapy for is rated as insufficient.

The effect of four other psychological and behavioral interventions on loudness was examined.[37,44,46,58] A significant effect of treatment on subjective loudness was reported for an intervention using a self-help book with telephone therapy; no significant effects of treatment were reported for education interventions[37,46] or for yoga.[47] SOE was rated as insufficient given the high risk of bias and small sample sizes.

Sleep Disturbance

Five RCT studies with waitlist controls investigated the effects of interventions on sleep as a secondary outcome measure.[23,44,47,67,69] Four RCTs[23,47,67,69] examined CBT, and a statistically significant benefit for biofeedback-based CBT was seen in one study.[67] The SOE for CBT interventions for the outcome of sleep disturbance is rated as insufficient. Other interventions that had a statistically significant improvement in sleep were the self-help book with telephone therapy[44] and ACT[69]. No benefit from TRT,[69] TCT,[47] or yoga[47] was found. The SOE for TRT and other interventions is rated as insufficient.

Anxiety Symptoms

Five RCT studies[23,24,42,44,69] evaluated anxiety symptoms. CBT delivered over the Internet[23] and CBT delivered to a small group[24] have beneficial effects on anxiety, but these effects are not significant and the studies have moderate risk of bias. There is low SOE that CBT interventions decrease anxiety symptoms relative to inactive comparator interventions.

There seems to be a moderate beneficial effect of ACT on anxiety,[69] but this study also has a high risk of bias. Relaxation[42] and TRT[69] seem to have little or no beneficial effect on anxiety. For TRT therapy, relaxation therapy, and "other" interventions, only single studies were evaluated and as such the consistency is unknown; the studies have wide confidence intervals and very small sample sizes and are therefore imprecise. Dose response cannot be assessed and risk of publication bias is high for these interventions given the small sample sizes.

Depression Symptoms

Eleven RCTs[23,24,37,38,42,44,46,47,60,67,69] investigated the effects of treatments on depressive symptoms by comparing treatments to waitlist controls. Seven studies[23,24,37,38,46,47,67] evaluated CBT interventions and the outcome of depressive symptoms. The findings favored the CBT treatment in all but one study; only one study showed statistical differences and the remaining studies did not. The SOE was low for CBT interventions decreasing depression symptoms relative to inactive controls.

The effect of TRT on depressive symptoms was evaluated in one study,[69] but no significant effects were found. For relaxation therapies all three studies[60,46,42] favored treatment but none were statistically significant. All these studies were at high risk of bias, and the SOE for relaxation interventions is rated as insufficient.

Five studies[37,44,46,47,69] investigated the effects of other treatments on depressive symptoms. Treatment involving a self-help book and telephone therapy helped improve depression;[44] no benefit was seen for ACT,[69] education,[46,37] or yoga.[47] When considering the interventions grouped in the "other category", we deemed the evidence as insufficient given the high risk of bias for all studies, unknown consistency, and small sample sizes.

Global Quality of Life

Six RCT studies[46,47,49,58,67,69] investigated the effects of treatments on global QoL by comparing treatments to waitlist controls. Five interventions were included in the CBT category. The only statistically significant effect favoring CBT was an intervention using biofeedback-based CBT.[67] The SOE for CBT interventions for the outcome of depression symptoms is rated as insufficient.

TRT[69] and relaxation[46] were each evaluated in one study, and no significant effect of treatment was reported. Four other psychological and behavioral treatments (ACT[69], bibliotherapy,[49] education with minimal contact,[46] and yoga[47]) were evaluated. No significant effects of treatment on global QoL were reported for ACT,[69] education,[46] or yoga.[47] A small effect size was reported for bibliotherapy.[49] For TRT interventions, relaxation therapy, and "other category" interventions, we deemed the evidence as insufficient given the high risk of bias, unknown inconsistency, wide confidence intervals, and small sample sizes.

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 and Conclusions

In a rehabilitative context, discomfort from tinnitus is more often the reason for seeking medical attention than hearing loss. 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.[8] Tinnitus is a complex condition for which a variety of interventions (some tinnitus-specific and others generic) have been applied. This comparative evidence review demonstrates the significant research gaps with respect to KQ1 (methods to identify those for further evaluation or treatment) and KQ3 (prognostic factors). We focus the discussion on evaluating the efficacy of different interventions (KQ2).

When considering the applicability of study findings in general, the study populations were relatively homogenous and were limited to predominately middle aged (≥50 years of age) persons suffering from predominantly subjective idiopathic tinnitus of mild to moderate severity. We cannot draw conclusions about the efficacy of the therapies in persons younger than 42 years of age, despite the fact that a recent survey estimated tinnitus was prevalent in 12.2 percent of the U.S. population under 44 years of age.[59,93] It also 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.[94] This suggested that reports of tinnitus tended to increase with more recent birth cohorts compared with earlier birth cohorts; participants in a given generation were significantly more likely to report tinnitus than participants from a generation 20 years earlier (odds ratio [OR]=1.78; 95% confidence interval (CI), 1.44 to 2.21).

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[31,34,54] and even to 18 months for one study.[40] 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 weeks[60] to two months,[42] or three months[24,27,47] to six months,[38] but most continued to one year[23,37,39,44,46,49] or even 18 months.[69] 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 and behavioral therapies, which are usually provided by rehabilitative professionals, such as audiologists and psychologists, whose practices may put greater emphasis on establishing as well as maintaining change due to an intervention.

Most 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.[23] 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.

Key Question 2

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, 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; this 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 studies eligible for this question; moreover, specific adaptations of measures validated in non-tinnitus populations (i.e., study-specific VAS) 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 and Food Supplement Interventions

A total of 16 unique studies (17 publications)[21,25,26,32,35,41,43,51,52,55,57,59,61,62,65,68,71] evaluated the efficacy of pharmacological interventions or food supplements in tinnitus. The included articles evaluated 14 different interventions, all of which were compared to 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 did show statistically significant effects on some outcomes: nortriptyline[62] and honeybee larvae[25] for depression; alprazolam[43] and zinc[26] for loudness; and acamprosate[21] for tinnitus-specific QoL measured as "disturbance." One study[62] found conflicting results for tinnitus-specific QoL (e.g., improved QoL or no difference compared to placebo) 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 depressive symptoms, although the reduction failed to reach statistical significance at the 5% level on one of the three scales used to measure depression.

Overall, we found little evidence to suggest that the therapies led to improvements over placebo on any of these outcomes. Our results are in agreement with the conclusions of previous systematic reviews, which found insufficient, inconsistent, or no evidence of treatment effects.[95-100]

In terms of SOE, we have low confidence in 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.

Table ES-2 shows the SOE for three of the seven outcomes evaluated in this review. The SOE was low or insufficient for all of the pharmacological and food supplement interventions. SOE was assessed for the adverse event of sedation only.

Table ES-2. Strength of Evidence: Studies that evaluate pharmacological interventions compared to inactive control reporting depression symptoms AND tinnitus-specific quality of life outcomes

Outcome Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the effect SMD range (CI)	SOE
T-S QOL Anti-depression	N/A	4[32,41,59,62,71*]	Medium	Inconsistent	Direct	Imprecise	-0.61 (-1.03 to -0.19) to 0.12 (-0.31 to 0.54)	Low
T-S QOL Psychoactive drugs	N/A	3[21,55,68]	Medium	Inconsistent	Direct	Imprecise	-1.57 (-2.28 to -0.86) to -0.01 (-0.38 to 0.35)	Low
T-S QOL Other drugs	MEP, vardenafil, Deanxit	3[51,52,65]	Medium	Inconsistent	Direct	Imprecise	-0.68 -1.21 to -0.16) to 0.35 -0.26 to 0.86)	Low
T-S QOL Food supplement	N/A	3[25,35,57]	Medium	Inconsistent	Direct	Imprecise	-0.21 (-0.72 to 0.30) to -0.21 -0.72 to 0.30)	Low
Depression Anti-depressants	Sertraline Paroxetine Nortriptyline	3[59,62,71]	Medium	Inconsistent	Direct	Imprecise	-1.13 (-1.57 to -0.69) to 0.21 (-0.16 to 0.57)	Low
Depression Other drugs	Deanxit	1[52]	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study[52])	Direct	Imprecise		Insufficient
Depression Food supplement	Honeybee larvae vs. hydrogenated dextrin	1[25]	Medium	Unknown (single study)	Direct	Imprecise	-0.49 (-1.01 to 0.04)	Insufficient

*four studies, five publications

Abbreviations: ACT = acceptance and commitment therapy; BLT = bibliotherapy; BPT = brief phone therapy; CBT = cognitive behavioral training; CI = confidence interval; EM = electromagnetic; 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; T-S QOL -= tinnitus-specific quality of life; WLC = wait list control

Medical Interventions

Eleven studies evaluated four different types of medical interventions that included rTMS,[22,28,48,50,56] electromagnetic stimulation,[36] low level laser therapy (LLLT),[30,53,64] acoustic coordinated reset neuromodulation (ACRN),[63] and acupuncture.[66] Almost all studies in this grouping evaluated tinnitus-specific QoL. In general, SOE for tinnitus-related QoL 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. 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.

When considering the individual types of interventions and efficacy with respect to tinnitus related QoL, 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 tinnitus-specific QoL scores) occurred with low frequency rTMS (1 Hz) at up to 6 months followup[22] but this single study was at high risk of bias. Our review also showed that adverse events were generally poorly evaluated and reported. A previous systematic review[101] 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.

With respect to the interventions of ACRN, LLLT, and acupuncture, SOE was rated as insufficient for tinnitus-specific QoL.

When considering the outcome of perceived loudness, there were only five trials that evaluated this outcome[28,53,63,64,66] 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.

One intervention (ACRN) did show small differences for one stimulation parameter compared to sham stimulation.[63] 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;[53] we judged this trial to have insufficient SOE. No studies evaluated the effect on sleep disturbance and global QoL with these interventions.

Table ES-3 shows the SOE for three of the seven outcomes evaluated in this review. The SOE was insufficient for all of the medical interventions; sedation was not an adverse event related to these 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.

Table ES-3. Strength of Evidence: Studies that evaluate medical interventions compared to inactive control reporting depression symptoms AND 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
T-S QOL rTMS vs. sham		4[22,28,50,56]	High	Inconsistent	Direct	Imprecise	-1.23 (-2.16,-0.30) to-0.02 -0.67, 0.72)	Insufficient
T-S QOL Hi-frequency EM energy vs. sham		1[36]	High	Unknown	Direct	Imprecise	-0.13 (-0.86, 0.60)	Insufficient
T-S QOL ACRN vs. sham		1[63]	High	Unknown	Direct	Imprecise	-0.50 -1.56, 0.56) to -0.03 (-1.07, 1.02)	Insufficient
T-S QOL Laser therapy vs. sham		2[53,64]	High	Inconsistent	Direct	Imprecise	-0.00 -0.54, 0.53) to 0.33 (-0.29, 0.94)	Insufficient
T-S QOL Acupuncture vs. placebo		1[66]	High	Unknown	Direct	Imprecise	-0.10 (-0.63, 0.10)	Insufficient
Depression Laser therapy vs. sham		1[53]	High	Unknown	Direct	Imprecise	0.33 (-0.24, 0.89)	Insufficient

Abbreviations: ACT = acceptance and commitment therapy; BLT = bibliotherapy; BPT = brief phone therapy; CBT = cognitive behavioral training; CI = confidence interval; EM = electromagnetic; 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; T-S QOL -= tinnitus-specific quality of life; WLC = wait list control

Studies Involving Sound Technologies

Four unique RCTs[31,34,40,54] and a related study[33] were eligible for this intervention category. All studies evaluated the relative effectiveness of various sound-based interventions 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. All of these studies were published within the last 15 years. It is noteworthy that all of the papers reviewed for this category of intervention were head to head trials, possibly reflecting the relative maturity of sound-based interventions in audiology.

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 pharmacological and medical interventions also apply to this category of intervention. Two recent systematic reviews evaluating a different set of eligible studies derived similar conclusions, remarking upon the diversity of interventions[96] and suggesting insufficient evidence.[95,96]

Studies Involving Psychological and 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 moderate strength for CBT and coping approaches, suggesting moderate confidence that the studies evaluating these interventions reflect the true effect for the two outcomes of importance analyzed (i.e., tinnitus-specific QoL and sleep). Note that the apparent absence of benefits from treatment for outcomes related to anxiety and depressive symptoms may not be meaningful given that most of the participants in the studies had no more than mild symptoms pretreatment. Recent systematic reviews have evaluated tinnitus-specific QoL and CBT-related interventions and rated the evidence as moderate[95] or showed evidence of benefit.[95,96,102,103] One of these previous reviews suggest that the evidence shows that CBT interventions do not affect depression and anxiety symptoms,[96] and other reviews suggest that the evidence demonstrates that CBT improves depression scores[102] or mood.[103] One review showed no evidence of CBT affecting subjective loudness.[102]

Behavioral interventions (i.e., relaxation, education, TRT) employed an isolated approach that did not confer the same degree of benefit and were rated as low SOE, being plagued with the same problems as the studies evaluating pharmacological and medical interventions. It was observed that CBT combined with other behavioral interventions were common treatment options. It is interesting that the development of progressive[104,105] or staged treatments is active,[29] which could 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 multi-modal interventions.

Four subcategories of psychological and behavioral interventions were examined: CBT (n=8) and related treatments, TRT-related treatments (n=2), treatments involving primarily relaxation (n=3), and other interventions (n=7), including two involving reading tinnitus books, two emphasizing education, one with yoga, one with Qigong, and one with ACT. Outcomes for tinnitus-specific QoL (19 treatments), subjective loudness (13 treatments), sleep disturbance (6 treatments), anxiety (9 treatments), depressive symptoms (17 treatments), and global QoL (8 treatments) were measured using a large variety of measures. The SOE for psychological and behavioral interventions was rated as low for the outcomes of anxiety and depression symptoms. Low SOE indicates that future research will likely change the magnitude and possibly the direction of the observed effects. Interventions involving CBT for the outcome of tinnitus-specific QoL and perceived loudness were deemed to have moderate SOE, suggesting that the impact of future research will likely change the magnitude of the effect size to a lesser degree than the other interventions. Adverse events were largely not reported in this intervention group. Some studies reported an absence of adverse events, 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.

Table ES-4 shows the SOE for three of the seven outcomes evaluated in this review. Sedation was not an adverse event related to these interventions.

Table ES-4. Strength of Evidence: Studies that evaluate psychological/behavioral interventions compared to inactive control reporting depression symptoms AND 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
T-S QOL CBT/ CBT combination vs. WLC or no treatment	N/A	8[23,24,37,38,46,47,58,67]	High	Consistent	Direct	Imprecise	-1.56 (-1.98,-1.13) to -0.13 (-0.93, 0.67)	Moderate
T-S QOL TRT vs. WLC or no treatment	N/A	2[39,69]	High	Inconsistent	Direct	Imprecise	-0.60 (0-0.93,-0.26) to -0.12 (-0.46, 0.23)	Insufficient
T-S QOL Relaxation vs. WLC	N/A	3[42,46,60]	High	Inconsistent	Direct	Imprecise	-1.02 (-2.20, 0.17) to 0.17 (-1.02, 1.36)	insufficient
T-S QOL Other psych / behavioral	MC-E vs. WLC	1[46]	High	Unknown	Direct	Imprecise	-0.38 (-1.05, 0.28)	Insufficient
	Self-help and BPT vs. WLC	1[44]	High	Unknown	Direct	Imprecise	-0.64 (-1.16, -0.12)	Insufficient
	ACT vs. WLC	1[69]	High	Inconsistent	Direct	Imprecise	-1.12 (-1.76, -0.48)	Insufficient
	BLT vs. WLC	1[49]	High	Unknown	Direct	Imprecise	-0.33 (-0.68, 0.02)	Insufficient
	Qigong training vs. WLC	1[27]	High	Unknown	Direct	Imprecise	-0.14 (-0.82, 0.54)	Insufficient
	Yoga vs. WLC	1[47]	High	Unknown	Direct	Imprecise	-0.17 (-0.96, 0.63)	Insufficient
Depression CBT/ CBT combination vs. WLC or no treatment	N/A	7[23,24,37,38,46,47,67]	High	Consistent	Direct	Imprecise	-1.05 (-1.92, -0.19) to -0.04 (-0.57, 0.49)	LOW
Depression TRT vs. WLC or no treatment	N/A	1[69]	High	Unknown	Direct	Imprecise	0.05 (-0.55, 0.66)	Insufficient
Depression Relaxation vs. WLC	N/A	3[42,46,60]	High	Inconsistent	Direct	Imprecise	-1.85 (-3.59, -0.11) to -0.06 (-1.24, 1.13)	insufficient

Table ES-4. Strength of Evidence: Studies that evaluate psychological/behavioral interventions compared to inactive control reporting depression symptoms AND tinnitus-specific quality of life outcomes (cont'd)

Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the effect SMD range (CI)	SOE
Depression Other psychological	ACT vs. WLC	1[69]	High	Unknown	Direct	Imprecise	-0.19 (-0.78, 0.40)	Insufficient
	Self-help and BPT vs. WLC	1[44]	High	Unknown	Direct	Imprecise	-0.54 (-1.06, -0.02)	Insufficient
	MC-E vs. WLC	1[46]	High	Unknown	Direct	Imprecise	-0.31 (-0.97, 0.35)	Insufficient
	Education vs. WLC	1[37]	High	Unknown	Direct	Imprecise	0.08 (-0.54, 0.70)	Insufficient
	Yoga vs. WLC	1[47]	High	Unknown	Direct	Imprecise	-0.32 (-1.12, 0.48)	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; SSRI = serotonin reuptake inhibitors; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Future Research Recommendations

Future research should attempt to incorporate the following recommendations for primary studies evaluating patients with subjective idiopathic tinnitus.

Key Question 1

1. Studies should be developed to evaluate the comparative effectiveness of instruments used to assess the severity and status of subjective idiopathic tinnitus

Key Question 2

Population

1. Include a broader representation of adult patients with respect to age (range of middle age to old/elderly), sex (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 cointerventions, including complementary and alternative medicine therapies that have the potential to confound and contaminate study interventions

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, sex, 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. Length of followup should be long enough to study medium- to long-term outcomes given the chronicity of tinnitus (e.g., the maximum length of followup in the pharmacological/food supplement group of studies was 16 weeks, which is is inadequate to assess the durability of treatment over time)

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

Outcomes

1. Identify primary and secondary outcomes within the studies
2. Consider the inclusion of patient-reported outcomes using scales with established psychometric properties, including responsiveness, in the idiopathic tinnitus population
3. Assess the validity and responsiveness of outcome measurement instruments (e.g., VAS) in persons with tinnitus prior to using these instruments to evaluate the efficacy of tinnitus interventions
4. Ensure back translation of outcome measurement instruments prior to use in languages other than the language of development.
5. Measure global QoL to capture how persons value the risk-benefit trade-off between the efficacy and adverse effects profiles of treatments under evaluation
6. Conform to the Consolidated Standards of Reporting Trials (CONSORT)[106] 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 trials may be required to capture harms adequately

Other

1. To 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 RCTs 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
2. 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

Key Question 3

1. Studies should be developed to evaluate the natural history and prognostic factors in persons with subjective idiopathic tinnitus

Executive Summary References

1. American Tinnitus Association. Top 10 most frequently asked questions. www.ata.org/for-patients/faqs.

2. Davis A, El Rafaie A. Epidemiology of tinnitus. In: Epidemiology of tinnitus, Tyler RS,ed. San Diego,CA: Singular Publishing Group; 2000. 1 p. 1-24.

3. Henry,J.A. 2011 Jul 26; Key informant interview.

4. Henry JA, Zaugg TL, Myers PJ, et al. A triage guide for tinnitus. J Fam Pract. 2010;59(7):389-93. PMID:20625568

5. Tuz HH, Onder EM, Kisnisci RS. Prevalence of otologic complaints in patients with temporomandibular disorder. Am J Orthod Dentofacial Orthop. 2003;123(6):620-3. PMID:12806339

6. Ash CM, Pinto OF. The TMJ and the middle ear: Structural and functional correlates for aural symptoms associated with temporomandibular joint dysfunction. Int J Prosthodont. 1991;4(1):51-7. PM:2012671

7. Davis PB, Wilde RA, Steed LG, et al. Treatment of tinnitus with a customized acoustic neural stimulus: A controlled clinical study. Ear Nose Throat J. 2008;87(6):330-9. PMID:18561116

8. Davis A, Smith P, Ferguson M, et al. Acceptability, benefit and costs of early screening for hearing disability: A study of potential screening tests and models. Health Technol Assess. 2007;11(42):iii-294 PMID:17927921

9. Searchfield G. A commentary on the complexity of tinnitus management: Clinical guidelines provide a path through the fog. Eval Health Prof. 2011; PM:21224266

10. Department of Health. Provision of services for adults with tinnitus: A good practice guide. London: Central Office of Information; 2009.

11. Hoare DJ, Gander PE, Collins L, et al. Management of tinnitus in English NHS audiology departments: An evaluation of current practice. J Eval Clin Pract. 2010; PM:21087449

12. Henry JA, Schechter MA, Loovis CL, et al. Clinical management of tinnitus using a "progressive intervention" approach. J Rehabil Res Dev. 2005;42(4:Suppl 2):95-116. PMID:16470467

13. Juni P, Holenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: Empirical study. Int J Epidemiol. 2002;31(1):115-23.

14. Moher D, Pham B, Klassen T, et al. What contributions do languages other than English make on the results of meta-analysis? J Clin Epidemiol. 2000;53(9):964-72.

15. Wells, G. A., Shea, B., O'Connell, D. et al. The Newcastle-Ottawa Scale (NOW) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

16. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17(1):1-12. PM:8721797

17. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207.

18. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-care program. J Clin Epidemiol. 2010;63(5):513-23. PM:19595577

19. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144(6):427-37. PM:16549855

20. Abbott JA, Kaldo V, Klein B, et al. A cluster randomised trial of an internet-based intervention program for tinnitus distress in an industrial setting. Cognit Behav Ther. 2009;38(3):162-73. PMID:19675959

21. Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: Double-blind study. Revista Brasil Otorrinolaringol. 2005;71(5):618-23. PMID:16612523

22. Anders M, Dvorakova J, Rathova L, et al. Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: A randomized, placebo controlled study. Neuroendocrinol Lett. 2010;31(2):238-49. PMID:20424590

23. Andersson G, Stromgren T, Strom L, et al. Randomized controlled trial of internet-based cognitive behavior therapy for distress associated with tinnitus. Psychosom Med. 2002;64(5):810-6. PMID:12271112

24. Andersson G, Porsaeus D, Wiklund M, et al. Treatment of tinnitus in the elderly: A controlled trial of cognitive behavior therapy. Int J Audiol. 2005;44(11):671-5. PMID:16379495

25. Aoki M, Wakaoka Y, Hayashi H, et al. Effect of lyophilized powder made from enzymolyzed honeybee larvae on tinnitus-related symptoms, hearing levels, and hypothalamus-pituitary-adrenal axis-related hormones. Ear Hear. 2012;33(3):430-6. PMID:21971082

26. Arda HN, Tuncel U, Akdogan O, et al. The role of zinc in the treatment of tinnitus. Otol Neurotol. 2003;24(1):86-9. PMID:12544035

27. Biesinger E, Kipman U, Schatz S, et al. Qigong for the treatment of tinnitus: A prospective randomized controlled study. J Psychosom Res. 2010;69(3):299-304. PMID:20708452

28. Chung HK, Tsai CH, Lin YC, et al. Effectiveness of theta-burst repetitive transcranial magnetic stimulation for treating chronic tinnitus. Audiol Neuro Otol. 2012;17(2):112-20. PMID:21865723

29. Cima RF, Maes IH, Joore MA, et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: A randomised controlled trial. Lancet. 2012;379(9830):1951-9. PM:22633033

30. Cuda D, De CA. Effectiveness of combined counseling and low-level laser stimulation in the treatment of disturbing chronic tinnitus. Int Tinnitus J. 2008;14(2):175-80. PMID:19205171

31. Davis PB, Paki B, Hanley PJ. Neuromonics tinnitus treatment: Third clinical trial. Ear Hear. 2007;28(2):242-59. PMID:17496674

32. Dib GC, Kasse CA, Alves de AT, et al. Tinnitus treatment with Trazodone. Revista Brasil Otorrinolaringol. 2007;73(3):390-7. PMID:17684661

33. Dineen R, Doyle J, Bench J. Managing tinnitus: A comparison of different approaches to tinnitus management training. Br J Audiol. 1997;31(5):331-44. PMID:9373742

34. Dineen R, Doyle J, Bench J, et al. The influence of training on tinnitus perception: An evaluation 12 months after tinnitus management training. Br J Audiol. 1999;33(1):29-51. PMID:10219721

35. Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: Double blind, placebo controlled trial. BMJ. 2001;322(7278):73 PMID:11154618

36. Ghossaini SN, Spitzer JB, Mackins CC, et al. High-frequency pulsed electromagnetic energy in tinnitus treatment. Laryngoscope. 2004;114(3):495-500. PMID:15091224

37. Henry JL, Wilson PH. The psychological management of tinnitus: Comparison of a combined cognitive educational program, education alone and a waiting list control. Int Tinnitus J. 1996;2:9-20.

38. Henry JL, Wilson PH. An evaluation of two types of cognitive intervention in the management of chronic tinnitus. Scand J Behav Ther. 1998;27(4):156-66.

39. Henry JA, Loovis C, Montero M, et al. Randomized clinical trial: Group counseling based on tinnitus retraining therapy. J Rehabil Res Dev. 2007;44(1):21-32. PMID:17551855

40. Hiller W, Haerkotter C. Does sound stimulation have additive effects on cognitive-behavioral treatment of chronic tinnitus? Behav Res Ther. 2005;43(5):595-612. PMID:15865915

41. Holgers K-M, Zoger S, Svedlund J. The impact of sertraline on health-related quality of life in severe refractory tinnitus: A double-blind, randomized, placebo-controlled study. Audiol Med. 2011;9(2):67-72.

42. Ireland CE, Wilson PH, Tonkin JP, et al. An evaluation of relaxation training in the treatment of tinnitus. Behav Res Ther. 1985;23(4):423-30. PMID:3896227

43. Johnson RM, Brummett R, Schleuning A. Use of alprazolam for relief of tinnitus. A double-blind study. Arch Otolaryngol Head Neck Surg. 1993;119(8):842-5. PMID:8343245

44. Kaldo V, Cars S, Rahnert M, et al. Use of a self-help book with weekly therapist contact to reduce tinnitus distress: A randomized controlled trial. J Psychosom Res. 2007;63(2):195-202. PMID:17662757

45. Kaldo V, Levin S, Widarsson J, et al. Internet versus group cognitive-behavioral treatment of distress associated with tinnitus: A randomized controlled trial. Behav Ther. 2008;39(4):348-59. PMID:19027431

46. Kroner-Herwig B, Frenzel A, Fritsche G, et al. The management of chronic tinnitus: Comparison of an outpatient cognitive-behavioral group training to minimal-contact interventions. J Psychosom Res. 2003;54(4):381-9. PMID:12670617

47. Kroner-Herwig B, Hebing G, van Rijn-Kalkmann U, et al. The management of chronic tinnitus--Comparison of a cognitive-behavioural group training with yoga. J Psychosom Res. 1995;39(2):153-65. PMID:7595873

48. Langguth B, Kleinjung T, Frank E, et al. High-frequency priming stimulation does not enhance the effect of low-frequency rTMS in the treatment of tinnitus. Exp Brain Res. 2008;184(4):587-91. PMID:18066684

49. Malouff JM, Noble W, Schutte NS, et al. The effectiveness of bibliotherapy in alleviating tinnitus-related distress. J Psychosom Res. 2010;68(3):245-51. PMID:20159209

50. Marcondes RA, Sanchez TG, Kii MA, et al. Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: A double-blind controlled, clinical and neuroimaging outcome study. Eur J Neurol. 2010;17(1):38-44. PMID:19614962

51. Mazurek B, Haupt H, Szczepek AJ, et al. Evaluation of vardenafil for the treatment of subjective tinnitus: A controlled pilot study. J Negative Results Biomed. 2009;8:3. PMID:19222841

52. Meeus O, De RD, Van de Heyning P. Administration of the combination clonazepam-Deanxit as treatment for tinnitus. Otol Neurotol. 2011;32(4):701-9. PMID:21358561

53. Mirz F, Zachariae R, Andersen SE, et al. The low-power laser in the treatment of tinnitus. Clin Otolaryngol Allied Sci. 1999;24(4):346-54. PMID:10472473

54. Parazzini M, Del B, Jastreboff M, et al. Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators. Int J Audiol. 2011;50(8):548-53. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2011208063&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=2576&accno=2011208063

55. Piccirillo JF, Finnell J, Vlahiotis A, et al. Relief of idiopathic subjective tinnitus: Is gabapentin effective? Arch Otolaryngol Head Neck Surg. 2007;133(4):390-7. PMID:17438255

56. Plewnia C, Vonthein R, Wasserka B, et al. Treatment of chronic tinnitus with theta burst stimulation: A randomized controlled trial. Neurology. 2012;78(21):1628-34. PMID:22539568

57. Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: A randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. Clin Otolaryngol Allied Sci. 2004;29(3):226-31. PMID:15142066

58. Rief W, Weise C, Kley N, et al. Psychophysiologic treatment of chronic tinnitus: A randomized clinical trial. Psychosom Med. 2005;67(5):833-8. PMID:16204446

59. Robinson SK, Viirre ES, Bailey KA, et al. Randomized placebo-controlled trial of a selective serotonin reuptake inhibitor in the treatment of nondepressed tinnitus subjects. Psychosom Med. 2005;67(6):981-8. PMID:16314604

60. Scott B, Lindberg P, Lyttkens L, et al. Psychological treatment of tinnitus. Scand Audiol. 1985;14(4):223-30.

61. Sharma DK, Kaur S, Singh J, et al. Role of acamprosate in sensorineural tinnitus. Indian J Pharmacol. 2012;44(1):93-6.

62. Sullivan M, Katon W, Russo J, et al. A randomized trial of nortriptyline for severe chronic tinnitus. Effects on depression, disability, and tinnitus symptoms. Arch Intern Med. 1993;153(19):2251-9. PMID:8215728

63. Tass PA, Adamchic I, Freund H-J, et al. Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor Neurol Neurosci. 2012;30(2):137-59.

64. Teggi R, Bellini C, Piccioni LO, et al. Transmeatal low-level laser therapy for chronic tinnitus with cochlear dysfunction. Audiol Neuro Otol. 2009;14(2):115-20. PMID:18843180

65. Topak M, Sahin-Yilmaz A, Ozdoganoglu T, et al. Intratympanic methylprednisolone injections for subjective tinnitus. J Laryngol Otol. 2009;123(11):1221-5. PMID:19640315

66. Vilholm OJ, Moller K, Jorgensen K. Effect of traditional Chinese acupuncture on severe tinnitus: A double-blind, placebo-controlled, clinical investigation with open therapeutic control. Br J Audiol. 1998;32(3):197-204. PMID:9710337

67. Weise C, Heinecke K, Rief W. Biofeedback-based behavioral treatment for chronic tinnitus: Results of a randomized controlled trial. J Consult Clin Psychol. 2008;76(6):1046-57. PMID:19045972

68. Westerberg BD, Roberson JB, Jr., Stach BA. A double-blind placebo-controlled trial of baclofen in the treatment of tinnitus. Am J Otol. 1996;17(6):896-903. PMID:8915419

69. Westin VZ, Schulin M, Hesser H, et al. Acceptance and commitment therapy versus tinnitus retraining therapy in the treatment of tinnitus: A randomised controlled trial. Behav Res Ther. 2011;49(11):737-47. PMID:21864830

70. Zachriat C, Kroner-Herwig B. Treating chronic tinnitus: Comparison of cognitive-behavioural and habituation-based treatments. Cognit Behav Ther. 2004;33(4):187-98. PMID:15625793

71. Zoger S, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering--A randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2006;26(1):32-9. PMID:16415703

72. Neri G, De SA, Baffa C, et al. Treatment of central and sensorineural tinnitus with orally administered Melatonin and Sulodexide: Personal experience from a randomized controlled study. Acta Otorhinolaryngol Ital. 2009;29(2):86-91. PMID:20111618

73. Figueiredo RR, Langguth B, Mello de OP, et al. Tinnitus treatment with memantine. Otolaryngol Head Neck Surg. 2008;138(4):492-6. PMID:18359360

74. Akkuzu B, Yilmaz I, Cakmak O, et al. Efficacy of misoprostol in the treatment of tinnitus in patients with diabetes and/or hypertension. Auris Nasus Larynx. 2004;31(3):226-32. PMID:15364356

75. Bayar N, Boke B, Turan E, et al. Efficacy of amitriptyline in the treatment of subjective tinnitus. J Otolaryngol. 2001;30(5):300-3. PMID:11771024

76. Dobie RA, Sakai CS, Sullivan MD, et al. Antidepressant treatment of tinnitus patients: Report of a randomized clinical trial and clinical prediction of benefit. Am J Otol. 1993;14(1):18-23. PMID:8424470

77. Suckfüll M, Althaus M, Ellers-Lenz B, et al. A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus. BMC Ear Nose Throat Disord. 2011;11(1):

78. Dehkordi MA, Abolbashari S, Taheri R, et al. Efficacy of gabapentin on subjective idiopathic tinnitus: A randomized, double-blind, placebo-controlled trial. Ear Nose Throat J. 2011;90(4):

79. Jakes SC, Hallam RS, McKenna L, et al. Group cognitive therapy for medical patients: An application to tinnitus. Cognit Ther Res. 1992;Vol16, pp67-82, 1992:67-82.

80. Herraiz C, Diges I, Cobo P, et al. Auditory discrimination training for tinnitus treatment: The effect of different paradigms. Eur Arch Otorhinolaryngol. 2010;267(7):1067-74. PMID:20044759

81. Olzowy B, Canis M, Hempel JM, et al. Effect of atorvastatin on progression of sensorineural hearing loss and tinnitus in the elderly: Results of a prospective, randomized, double-blind clinical trial. Otol Neurotol. 2007;28(4):455-8. PMID:17529847

82. Searchfield GD, Kaur M, Martin WH. Hearing aids as an adjunct to counseling: Tinnitus patients who choose amplification do better than those that don't. Int J Audiol. 2010;49(8):574-9. PMID:20500032

83. Mason JD, Rogerson DR, Butler JD. Client centred hypnotherapy in the management of tinnitus--Is it better than counselling? J Laryngol Otol. 1996;110(2):117-20. PMID:8729491

84. Pandey S, Mahato NK, Navale R. Role of self-induced sound therapy: Bhramari Pranayama in Tinnitus. Audiol Med. 2010;8(3):137-41.

85. Erlandsson SI, Rubinstein B, Carlsson SG. Tinnitus: Evaluation of biofeedback and stomatognathic treatment. Br J Audiol. 1991;25(3):151-61. PMID:1873582

86. Bonaconsa A, Mazzoli MM, Antonia M, et al. Posturography measures and efficacy of different physical treatments in somatic tinnitus. Int Tinnitus J. 2010;16(1):44-50. PMID:21609913

87. Neri G, Baffa C, De SA, et al. Management of tinnitus: Oral treatment with melatonin and sulodexide. Journal of Biological Regulators & Homeostatic Agents. 2009;23(2):103-10. PMID:19589291

88. Lindberg P, Scott B, Melin L, et al. The psychological treatment of tinnitus: An experimental evaluation. Behav Res Ther. 1989;27(6):593-603. PMID:2692553

89. Gungor A, Dogru S, Cincik H, et al. Effectiveness of transmeatal low power laser irradiation for chronic tinnitus. J Laryngol Otol. 2008;122(5):447-51. PMID:17625032

90. Roland NJ, Hughes JB, Daley MB, et al. Electromagnetic stimulation as a treatment of tinnitus: A pilot study. Clin Otolaryngol Allied Sci. 1993;18(4):278-81. PMID:8877185

91. Khedr EM, Rothwell JC, Ahmed MA, et al. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: Comparison of different stimulus frequencies. J Neurol Neurosurg Psychiatry. 2008;79(2):212-5. PMID:18202212

92. Podoshin L, Ben-David Y, Fradis M, et al. Idiopathic subjective tinnitus treated by biofeedback, acupuncture and drug therapy. Ear Nose Throat J. 1991;70(5):284-9. PMID:1914952

93. Kochkin S, Tyler R, Born J. MarkeTrak VIII: The prevalence of tinnitus in the United States and the self-reported efficacy of various treatments. Hear Rev. 2011;18(12):10-27.

94. Nondahl DM, Cruickshanks KJ, Huang GH, et al. Generational differences in the reporting of tinnitus. Ear Hear. 2012;33(5):640-4. PM:22588269

95. Savage J, Waddell A. Tinnitus. Clinical Evidence. 2012;2012,2012 PMID:22331367

96. Hoare DJ, Kowalkowski VL, Kang S, et al. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. Laryngoscope. 2011;121(7):1555-64. PMID:21671234

97. Hoekstra CE, Rynja SP, van Zanten GA, et al. Anticonvulsants for tinnitus. Cochrane Database Syst Rev. 2011;(7):CD007960. PMID:21735419

98. Karkos PD, Leong SC, Arya AK, et al. 'Complementary ENT': A systematic review of commonly used supplements. J Laryngol Otol. 2007;121(8):779-82. PMID:17125579

99. Hilton, Malcolm P, Stuart, et al. Ginkgo biloba for tinnitus. Cochrane Database Syst Rev. 2010;(3):

100. Baldo, Paolo, Doree, et al. Antidepressants for patients with tinnitus. Cochrane Database Syst Rev. 2009;(1):

101. Meng Z, Liu S, Zheng Y, et al. Repetitive transcranial magnetic stimulation for tinnitus. Cochrane Database Syst Rev. 2011;(10):CD007946 PMID:21975776

102. Martinez-Devesa P, Perera R, Theodoulou M, et al. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev. 2010;(9):CD005233. PMID:20824844

103. Hesser H, Weise C, Westin VZ, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. Clinical Psychology Review. 2011;31(4):545-53. PMID:21237544

104. Henry JA, Zaugg TL, Myers PJ, et al. The role of audiologic evaluation in progressive audiologic tinnitus management. Trends Amplification. 2008;12(3):170-87. PMID:18628281

105. Henry JA, Zaugg TL, Myers PJ, et al. Progressive audiologic tinnitus management. ASHA Leader. 2008;13(8):14-7.

106. Ioannidis JPA, Evans SJW, Gotzsche PC, et al. Better reporting of harms in randomized trials: An extension of the CONSORT statement. Ann Intern Med. 2004;141(10):781-8.

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Introduction

Background

Tinnitus is a symptom and not a disease. Tinnitus is the perception of sound in the absence of an external auditory stimulus. It 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 (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.[1] The prevalence of tinnitus increases with age and noise exposure.[2] In turn, 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.[3] 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.[1] Traumatic brain injury (concussion) is a common cause of tinnitus. 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.[4] These effects may be temporary, but can be permanent, especially with respect to aminoglycoside antibiotics and cancer chemotherapeutics, in particular cisplatin.

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.[5-7] It is often regarded as a "chronic stressor, creating a vicious circle of stress and exacerbation of tinnitus."[8]

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 defined as tinnitus that is perceptible by both patient and examiner. Subjective tinnitus is idiopathic and perceptible only by the patient. Due to the rarity of objective tinnitus, some investigators have argued that all tinnitus is subjective and should instead be classified by origin, either as somatic or neurophysiologic.[9]

In this classification, *somatic tinnitus* is categorized as tinnitus with an underlying medical condition that creates internal acoustic mechanical sounds; in this case, the tinnitus has a vascular, muscular, respiratory, or temporomandibular joint (TMJ) origin.[10] 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.[10] 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.[11]

In this review, the term *subjective idiopathic tinnitus* will be used rather than neurophysiologic tinnitus because it is the term more commonly used in the literature at this time to describe the same condition. This is the most commonly diagnosed type of tinnitus.[10] 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.[12] 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 being predominantly a psychological problem.[13-15]

Measurement

It is essential to distinguish chronic tinnitus from temporary ear noises (sudden, unilateral, tonal sounds that typically last for up to a minute before decaying) that would not be considered pathological. 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 six months.[10]

Various measures can be used to evaluate the presence and severity of the tinnitus.[16] 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.[17]

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.[18] 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. These and most other tinnitus questionnaires are, however, limited in that they were not designed nor validated to measure the effectiveness of tinnitus interventions.[19] Such effectiveness is referred to as "responsiveness," which emphasizes effect sizes, content validity, and response scaling that enables detection of change.[20,21] The Tinnitus Functional Index (TFI) is a new 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, and it has not yet been used to evaluate comparative effectiveness of treatments.[22]

Treatment

Following a medical examination, some patients with subjective idiopathic tinnitus may receive "no treatment" with education 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 the 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, the range of interventions can include, but is not limited to, pharmacological/food supplements, medical interventions, sound technologies, and psychological/behavioral interventions, as outlined below. 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.[23-27] See Table 1 for examples. These treatments have been indirect solutions because they focus on tinnitus-associated symptoms, such as depression symptoms, stress, or sleep disturbance.[28] 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.[29]

Table 1. Some pharmacological treatments for tinnitus

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

Abbreviations: Botox = botulinum toxin type A

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.[30]

Medical Interventions

Low Level Laser Treatments

Low level laser therapy (LLLT) has been used to treat tinnitus. It is assumed that laser irradiation can improve cell proliferation, increase blood flow in the inner ear canal, and activate cellular activities that repair hair cells.[31] 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 TMJ disease.[32] TMJ disease consists of a collection of medical and dental conditions that affect the TMJ, masticulatory muscles, and/or the adjoining structures and cause pain and tenderness, most frequently felt in the jaw and the temple but also in the ear and surrounding area.[33] 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).[34]

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) delivers an electrical field to the cerebral cortices modulating the excitability in the area of the cerebral cortex believed to be associated with tinnitus.[35] 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.[36]

Complementary and Alternative Medicine Therapies

Complementary and alternative medicine (CAM) therapies—including acupuncture, and hyperbaric oxygen—are another treatment option for patients with tinnitus. The use of acupuncture as a tinnitus treatment originated in East Asian countries and has since expanded to North America. This therapy is suggested to reduce discomfort associated with tinnitus when needles are applied to the hand and face on the affected side.[37]

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.[38] 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.

Individuals seeking general information about tinnitus relief on the Internet will find a large array of CAM approaches proposed to relieve and even “cure” tinnitus. These include, but are not limited to, diet modifications, such as 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.[39-41]

Sound Technologies

Hearing Aids, Cochlear Implants, 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 all of 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.[42]

Cochlear implants may reduce tinnitus because the tinnitus is masked by improving the perception of external sounds or through electrical stimulation of the auditory nerve, but are only appropriate for use by a very specific subset of patients (e.g., people who have bilateral profound sensorineural hearing loss).[36]

Tinnitus masking was developed in the 1970s. The original purpose was to 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.[43] This is done by using ear-level sound generators, often 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,[43] they are generally not covered under health insurance plans.[44]

Neuromonics Tinnitus Treatment

Neuromonics Tinnitus Treatment is a combination of acoustic stimulation with a structured program of counseling and support by a clinician who has been trained specifically in tinnitus rehabilitation.[45] 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."[46]

Psychological/Behavioral treatments

Cognitive Behavioral Therapy

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, but those who are most distressed by tinnitus may be psychologically vulnerable.[47] Interventions such as 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.[48] CBT 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.[49]

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.[50] Sound is also used with TRT, but for a completely 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."[51] 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.[50,51]

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.[15]

Educating patients about their tinnitus has been proposed to improve the management of tinnitus-related symptoms and their associated discomfort.[15] 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.[9]

Relaxation therapies also offer strategies to focus the patient's attention away from the sound, aiming to psychologically alleviate stress responses to tinnitus.[52] Although these therapies may not eliminate the tinnitus, they aim to improve the person's quality of life through habituation to decrease their 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. PTM uses elements of hearing aids, masking, TRT, and CBT. The key features of PTM are that it is a stepped-care approach, it is 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.[42,53] A similar progressive stage treatment approach has recently been developed by others.[54]

Scope and Key Questions

In a rehabilitative context, the discomfort of tinnitus is often more common than hearing loss in triggering people to seek hearing health care, yet typical audiological interventions focus on the remediation of hearing loss rather than on treatments for tinnitus.[55] 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.[56] 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*[49] for the commissioning of tinnitus services and for managing tinnitus from primary care onwards.[57] 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.[10,58]

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 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 (e.g., ringing in the ears, whooshing sounds).

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

Timing or Followup

No restrictions.

Setting

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

KQ2. In adults (18 and over) with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral intervention (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.

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.

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)
- Complementary and alternative medicine (CAM) therapies that are not food supplements; acupuncture; hyperbaric oxygen therapy; 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 Events

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

Excluded Adverse Effects

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); studies were not excluded for any study setting.

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

Population(s)

Adults 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 Events

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

Timing or Followup

No restrictions.

Setting

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

Analytic Framework

Following consultation with key informants, the AHRQ 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 key questions (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 following the analytic framework.

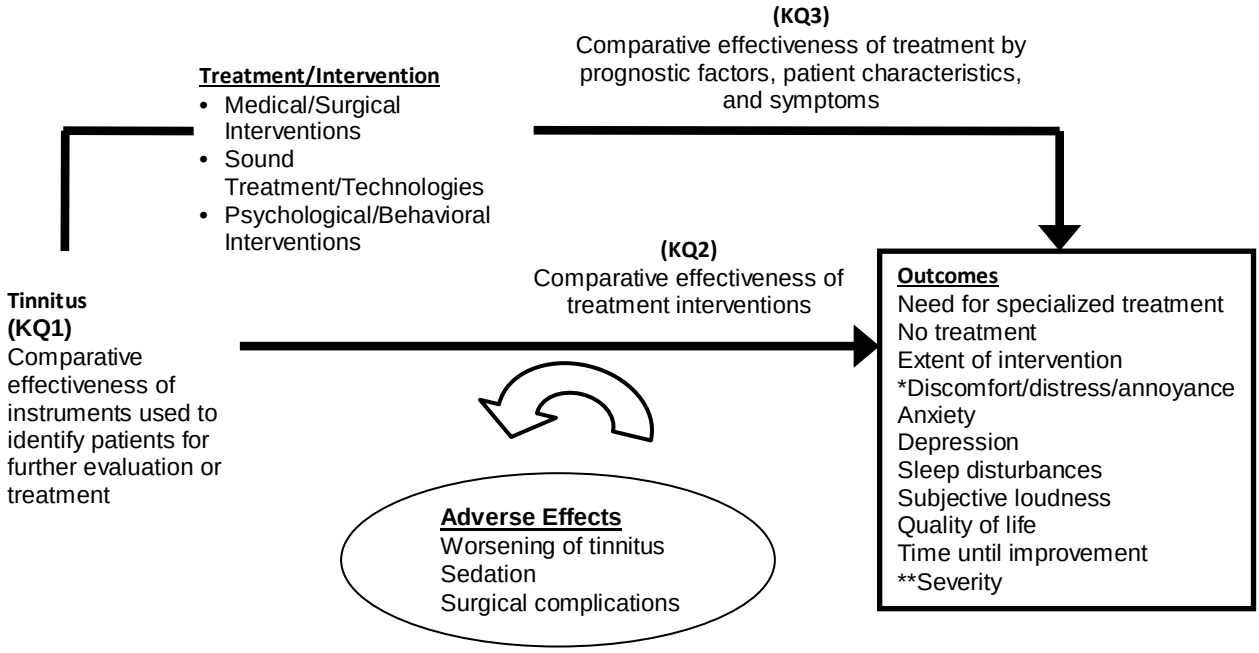


Figure 1. Analytic Framework

*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 Key Informants. Initially a panel of Key Informants gave input on the KQs to be examined; these KQs were posted on AHRQ's website for public comment for 4 weeks and revised as needed. We then drafted a protocol for the CER and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review.

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 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 done 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. Reference lists of all systematic reviews and meta-analyses (which were separately coded for retrieval during screening) were reviewed. Any potentially

relevant citations were cross-checked within the citation database. Any references not found within the database were retrieved 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 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.[59,60] 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 our 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	**KQ1:** Adult (≥18 yrs) patients who visit healthcare practitioners with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds) **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	• Subjects <18 years of age • Dx of pulsatile tinnitus • Unilateral cases with specific medical Dx (e.g., pulsatile tinnitus with acoustic neuroma) • Tinnitus as side effect of drugs • Nonhuman subjects
Interventions	**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) **KQ2:** Any treatment/therapy used to reduce/help cope with tinnitus including but not limited to **Pharmacological** • 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 **Medical** • Laser treatments • TMJ treatment: dental orthotics and self-care; surgery • Transcranial magnetic stimulation • Complementary and alternative medicine therapies: acupuncture; hyperbaric oxygen therapy; diet, lifestyle, and sleep modifications (e.g., caffeine avoidance, exercise) **Sound Treatments/Technologies** • Hearing aids, cochlear implants, sound generators/maskers • Neuromonics, Tinnitus Retraining Therapy **Psychological/Behavioral** • Cognitive behavioral therapy, biofeedback, education, relaxation therapies, Progressive Tinnitus Management **Combination Therapies** • Any combination of tinnitus interventions (e.g., pharmacological treatment with cognitive behavioral therapy) **KQ3:** Any treatment/therapy used to reduce/help/cope with tinnitus including but not limited to those described in KQ2	**KQ1:** Non direct observations **KQ2:** No exclusions for interventions **KQ3:** No exclusions for interventions
Comparators	**KQ1:** Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus **KQ2:** Inactive controls (including placebo; no treatment; wait list; sham interventions) Active controls (including treatment as usual; other intervention/treatments)	**KQ1:** No exclusions **KQ2:** No exclusions **KQ3:** No exclusions

Table 2. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Comparators (cont'd)	**KQ3:** • 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.	
Comparators	**KQ1:** Different clinical evaluation methods used to characterize a diagnosis and measure severity of subjective idiopathic tinnitus **KQ2:** Inactive controls (including placebo; no treatment; wait list; sham interventions) Active controls (including treatment as usual; other intervention/treatments) **KQ3:** • 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.	**KQ1:** No exclusions **KQ2:** No exclusions **KQ3:** No exclusions
Outcomes	**KQ1:** Final outcome: No treatment; need for specialized treatment (e.g., audiology, otolaryngology, neurology, mental health care); extent of intervention **KQ2: Tinnitus-specific Quality of Life,** Sleep disturbance, , depression symptoms, subjective loudness, Global quality of life, tinnitus severity, adverse events (worsening of tinnitus, sedation, surgical complications, other treatment emergent events) **KQ3:** Time until improvement, sleep disturbance, discomfort, anxiety symptom, depression symptoms, subjective loudness, quality of life, return to "normal" work, adverse events (worsening of tinnitus, sedation, surgical complications)	Studies where outcomes were reported on non-numeric scales (such as loudness in decibels [dB]). No other exclusions based on the type of study outcome.
Publication languages	English	Non-English
Study design	**All KQs:** • RCTs or observational 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)	**All KQs:** Studies where: • Only scatter plots and bar graphs (no numerical data) were reported in tables or text. • Effect size could not be estimated (i.e., only p values reported with no outcome measure data)

Table 2. Inclusion and exclusion criteria (continued)

Category	Inclusion Criteria	Exclusion Criteria
Study design (cont'd)		• Outcome was reported results only 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 **KQ2:** • Cross-over studies that did not report first period data • Nonrandomized studies with comparators (case series, before-after studies) and observational studies (case-control studies, cohort studies) • Systematic reviews and narrative reviews (excluded but evaluated for reference list review) • Case reports/studies, and case series Editorials, comments, letters, opinion pieces, and abstracts
Setting	Primary care; specialty care (audiology, otolaryngology, neurology, mental health)	
Other criteria	Studies must address one 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) **All KQs:** Treatment approaches for adults at risk for a tinnitus diagnosis	

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 analogue scale; yrs = years

Data Extraction

The Evidence-based Practice Center (EPC) 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 events 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.[60] 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 studies[61] and the Jadad scale for RCTs.[62] Additional items were needed for the Newcastle Ottawa Scale to describe the population for cohort studies (2 items) and three additional items for the Jadad scale. Each quality item was be 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 *Assessing Applicability When Comparing Medical Interventions: AHRQ and the Effective Health Care Program*.[63] 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 KQ.

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, we calculated the mean difference from pre- and post-treatment scores provided and standard deviation was computed using the following equation:

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

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

We used a correlation of 0.69 between pre-treatment (baseline) and post-treatment (final/endpoint) scores based on evidence from existing literature.[64,65] We also carried out a sensitivity of potential correlation factors (0.0, 0.3, 0.5) in which effect size estimates were found to be essentially unchanged. The Cochran's Q (α=0.10) and I^2 statistic were employed to quantify the statistical heterogeneity between studies, where $p<0.10$ indicates a high level of statistical heterogenity 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.[66] Several domains of quality across studies may influence the overall strength of evidence for these KQs, including

1. Risk of bias (how the study design and conduct may have contributed to systematic error). We judge this 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 is possible, then how widely the point estimate varies across studies and the degree of overlap between confidence intervals across studies was considered.[64] The importance of the direction relative to the magnitude of the effect will be judged for each group of interventions and outcomes.[67]
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).[67]
5. Other key domains (publication bias, dose-response association, existence of plausible unmeasured confounders, and strength of association [i.e., magnitude of effect]).

The strength of evidence was classified into four grades based on the AHRQ EPC Program approach: high, moderate, low, or insufficient.[66,68] We assessed the SOE for the six outcomes of benefit (tinnitus related quality of life, perceived loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global quality of life) and outcomes of harm (sedation only).

Judgment of study limitations was anchored by the presence of a minimum of one RCT with a good or rating (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 and wide confidence intervals, all the intervention groupings were ranked as being imprecise. Low SOE indicates that future research will likely change the magnitude and possibly the direction of the observed effects. Similarly, moderate SOE suggests moderate confidence that the evidence reflects the true effect and further research may require a change in the estimate of effect. For most interventions, fewer than 10 studies were eligible and as such publication bias could not be formally assessed using statistical approaches. We recognize that the risk of publication bias is greater for reviews that are based on small randomized trials.[69] Based on this potential risk, we assumed that all intervention groupings were at risk in this systematic review and rated all groupings as “suspected” for publication bias. We further considered whether the studies within each intervention grouping were sponsored by industry; when relevant we note this in the summary of the SOE.

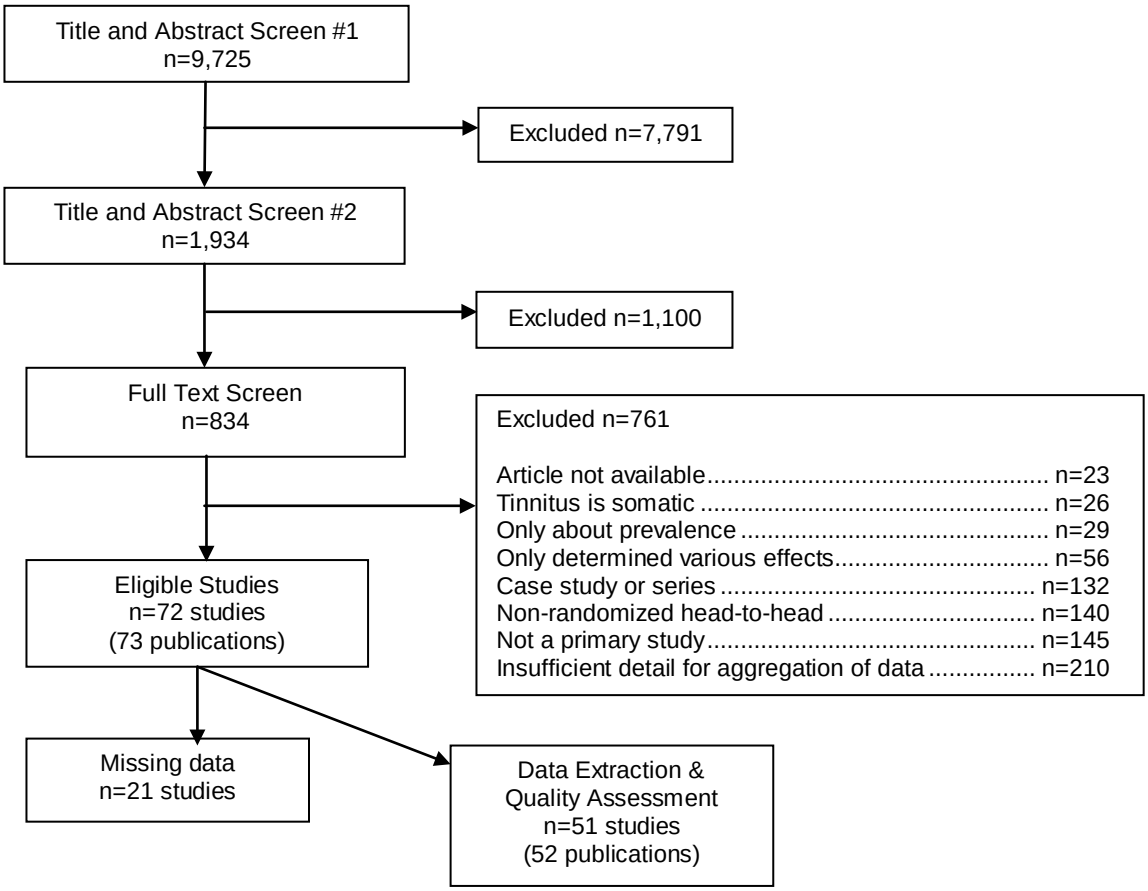
Peer Review and Public Comment

Experts in audiology, epidemiology, medical specialties, researchers and individuals representing stakeholder and user communities will be invited to provide external peer review of this CER; AHRQ task order officer and an associate editor also provided comments prior to submission for peer review. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We have endeavored to address all reviewer comments, revising the text as appropriate, and documenting everything in a disposition of comments report that 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).[70] 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 and 21 were not eligible for extraction. All studies were eligible for KQ2. Appendix C contains the list of studies excluded at full text screening.

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 (18 and over) with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of pharmacological/food supplement, medical/surgical, sound treatment/technological, or psychological/behavioral interventions (including combinations of interventions)?

A total of 51 studies (52 included publications)[7,13,14,24,31,46,52,54,71-114] address KQ2. We organized the eligible studies based on intervention groupings suggested by the Technical Expert Panel. Results for this 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, perceived loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global quality of life).

From these eligible studies, 21 studies were not included in the results presented because they did not present measures of variance[115-131] or presented results as proportions.[132-135] 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.

Results – Pharmacological or Food Supplement Interventions

Characteristics of Included Studies

A total of 17 articles[24,72,76,77,81,84,90,97,98,101,103,105-107,109,111,114] reported on 16 unique studies that evaluated interventions in the pharmacological or food supplement domain (See Appendix D. Table A). Two articles[90,114] pertained to the same study, with the followup publication[90] containing additional data on global quality-of-life (QoL) as an outcome.

Population Duration and Severity

In ten studies,[72,84,97,98,103,105,107,109,111,114] the majority of participants were male. The percentages of male participants in these studies ranged from 52 percent[107] to 89 percent.[98] Females formed the majority of participants in four studies,[76,77,81,101] ranging from 59 percent[77] to 79 percent.[76] One article[109] reported a male:female ratio of 2:1 in the active treatment group and 1.5:1 in the placebo group. Two publications[24,106] 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 42[114] to 63.[76] One study[81] 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.[24]

The largest study analyzed data for 708 participants at the end of followup.[84] The remaining 15 studies contained a mean of 62 participants, ranging in size from 28 persons[98] to 95 persons.[101]

Intervention

Four studies (five publications)[81,90,105,107,114] investigated anti-depressant drugs versus placebo. These drugs included sertraline,[90,114] paroxetine,[105] trazodone,[81] and nortriptyline.[107] Five publications[24,72,101,106,111] examined psychoactive (neurotransmitter) drugs versus placebo.

The psychoactive drugs were gabapentin,[101] baclofen,[111] alprazolam,[24] and acamprosate.[72,106] Three studies investigated other drugs, including methylprednisolone versus placebo,[109] vardenafil versus placebo,[97] and clonazepam plus Deanxit versus clonazepam plus placebo.[98] Four papers evaluated food supplements, with two[84,103] focused on gingko biloba, one[77] on zinc, and one[76] 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 weeks[111] and the longest was 16 weeks.[114]

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 Events
Anti-depressant drugs		**INACTIVE COMPARATOR**							
	1	Sertraline (SSRI antidepressant) vs. placebo Zoger,[114] 2006 and Holgers,[90] 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,[105] 2005	PSQI	HADS-A, BAI*	HADS-D, BDI*		QWB	THQ*, Likert-scale	yes
	3	Trazodone (SARI antidepressant) vs. placebo Dib,[81] 2007					VAS	VAS-s* VAS-d	yes
	4	Nortriptyline (2nd gen tricyclic antidepressant) vs. placebo Sullivan,[107] 1993		Sheehan's Disability	HDS			IOWA*, Likert-scale	yes
Psychoactive (Neuro-transmitter) drugs		**INACTIVE COMPARATOR**							
	1	Gabapentin (GABA analogue – GABAergic) vs. placebo Piccirillo,[101] 2007						THI	yes
	2	Baclofen (selective GABAB1 receptor agonist) vs. placebo Westerberg,[111] 1996				Subjective		THI	yes
	3	Alprazolam (benzodiazepine – anxiolytic) vs. placebo Johnson,[24] 1993				VAS			yes
	4	Acamprosate (glutamate antagonist & GABA agonist) vs. placebo Sharma,[106] 2012				VAS	Subjective		none
	5	Acamprosate vs. placebo Azevedo 2005,[72] 2005						Subjective	yes
Other drugs		**INACTIVE COMPARATOR**							
	1	Methylprednisolone (intratympanic injection) vs. placebo Topak,[109] 2009				Self-rated		TSI	yes
	2	Vardenafil (PDE5 inhibitor) vs. placebo Mazurek,[97] 2009	TQ-sub				SF-36	TQ	yes
	1	Clonazepam +Deanxit vs. Clonazepam +placebo Meeus,[98] 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 Events
Food Supplements		**INACTIVE COMPARATOR**							
		Gingko Biloba vs. placebo Rejali,[103] 2004					GHSI	THI	yes
		Gingko vs. Placebo: only effect size reported Drew,[84] 2001				VAS		TSQ (21-item)	yes
		Enzymolyzed honey bee larvae vs. placebo, Aoiki,[76] 2012			THI-subscale			THI, VAS	yes
		Zinc vs. placebo Arda,[77] 2003				Subjective			yes

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

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

Outcomes

Of the 6 outcomes of interest, tinnitus-specific QoL was evaluated in 13 studies,[72,76,81,84,97,98,101,103,105,107,109,111,114] subjective loudness in eight studies,[24,77,84,98,106,109,111,114] sleep disturbance in three studies,[97,98,105] anxiety symptoms in three studies,[105,107,114] depression symptoms in five studies,[76,98,105,107,114] and global QoL in six studies.[81,97,103,105,106,114] Adverse events were reported in all except two studies.[98,106] See Table 4.

Table 4. Outcome measures used in studies that evaluate pharmacological and food supplement interventions across the domains of interest

Outcome	Outcome Measurement Used
Sleep Disturbance	PSQI (Pittsburg Sleep Quality Index)[105] TQ-subscale (Tinnitus Questionnaire subscale – sleep disturbance)[97,98]
Anxiety Symptoms	HADS-A (Hospital Anxiety and Depression Scale – Anxiety subscale)[90,105] CPRS-S-A (Comprehensive Psychopathological Rating Scale – Anxiety subscale)[90] PGWB-subscale (Psychological General Well-being Index)[90] BAI (Beck Anxiety Inventory)[105] Sheehan's Disability Scale[107]
Depression Symptoms	HADS-D (Hospital Anxiety and Depression Scale – Depression subscale)[90,105] HDS (Hospital Depression Scale)[107] CPRS-S-A (Comprehensive Psychopathological Rating Scale – Anxiety subscale)[90] PGWB-subscale (Psychological General Well-being Index)[90] BDI (Beck Depression Inventory)[98,105] THI-subscale (Tinnitus Handicap Inventory subscale)[76]
Subjective loudness	VAS (Visual Analogue Scale)[24,84,90,98,106] Self-rated/subjective[77,109,111]
Global Quality of Life	PGWB (Psychological General Well-being Index)[90,114] QWB (Quality of Well-being Scale)[105] VAS (Visual Analogue Scale)[81] SF-36[97] GHSI (Glasgow Health Status Inventory)[103] Subjective/self-rated[106]
Tinnitus-Specific Quality of Life	TSQ (Tinnitus Severity Questionnaire)[84,90] THQ (Tinnitus Handicapped Questionnaire)[105] TQ (Tinnitus Questionnaire)[97,98] VAS (Visual Analogue Scale)[76,81,90,98] IOWA (IOWA disability scale)[107] THI (Tinnitus Handicap Inventory)[76,101,103,111] TSI (Tinnitus Severity Index)[109] Likert-scale[105,107] Subjective/self-rated[72]

Setting

Eleven studies[24,77,97,98,101,103,105-107,109,111,114] were set in specialty clinics (i.e., ear-nose-throat). Three studies[72,76,101] recruited participants through a university hospital, and another[84] through advertisements in the national press or a tinnitus publication.. One study[81] did not report its setting. See Appendix D. Table A.

Country

The studies were carried out in several different countries: Sweden;[90,114] the United States;[24,101,105,107,111] Brazil;[72,81] India;[106] Germany;[97] Belgium;[98] United Kingdom;[84,103] Japan;[76] and Turkey.[77,109] See Appendix D. Table A.

Sources of Funding

Sources of funding were not reported in seven studies.[24,72,77,81,103,106,109] Ten publications received funding from research councils, foundations, and government departments and non-profit associations.[76,84,90,97,98,101,105,107,111,114]

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 instance[76] 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.[84,97,101,103,105,114]

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. Seven studies[76,81,84,97,101,105,114] reported, and seven[24,72,98,103,106,107,111] did not report, the methods of allocation concealment. In two studies, we judged the methods to be inappropriate.[77,109]

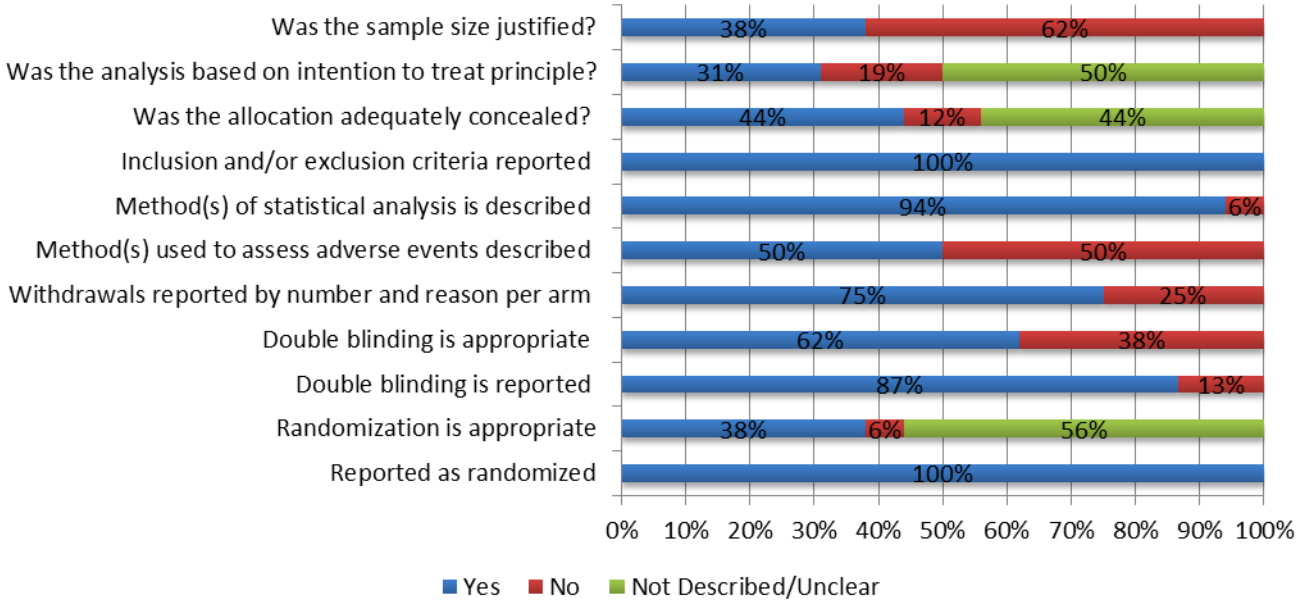
Fourteen studies contained specific mention of double-blinding. In four of these studies,[72,98,103,106] the authors did not provide sufficient detail for us to assess whether the methods of double-blinding were appropriate. The two studies without double-blinding included the methylprednisolone trial[109] (single-blinded) and one of the zinc studies[77] (no blinding reported whatsoever).

Only half the studies[24,84,97,101,105,109,111,114] 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,[136] 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[72,76,77,81,98,103,107] that did not delineate methods for assessing adverse effects did actually report such effects.

Five studies[97,101,105,111,114] 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.[137] 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[24,72,77,81,97,98,106,107,109,111] 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[72,98,107,114] assessed tinnitus-specific QoL by measuring discomfort, disturbance, or annoyance. Eleven studies[76,84,97,98,101,103,105,107,109,111,114] examined tinnitus-specific QoL by measuring severity. One study used both.[81]

All 5 studies[72,81,98,107,114] examining discomfort, disturbance, or annoyance used some form of visual analogue or Likert-type scale to measure the outcome. The sertraline study[114] used a 100 mm VAS and found no statistically significant difference between groups. The trazodone study[81] employed a 0- to 10-point scale and also found no difference between groups. Conversely, a paper[72] 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). In the Deanxit crossover trial,[98] 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).

The Deanxit study[98] 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 study[107] used a battery of instruments to measure discomfort. These instruments included the Multidimensional Pain Inventory (MPI) self and spouse evaluations,

two 0 to 7 VAS measuring 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; $p<0.05$).

Turning to the 12 studies[76,81,84,97,98,101,103,105,107,109,111,114] 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% level on the following instruments: Tinnitus Handicap Questionnaire (and a supplemental 8-point Likert scale, as well as the Disability Inventory),[105] 10-point VAS,[76,81] Iowa Disability Scale,[107] Tinnitus Handicap Inventory,[101,103,111] Tinnitus Severity Index,[109]Tinnitus Questionnaire,[97] and a 21-item severity questionnaire based on existing instruments.[84]

In the sertraline study,[114] 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,[98] 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; $p=0.001$).

Strength of Evidence – Tinnitus-specific Quality of Life

Strength of evidence (SOE) was low showing improvement in tinnitus-specific QoL in the case of each intervention group (antidepressants, psychoactive drugs, other and food supplements) relative to a placebo comparator (see Table 5). Effect sizes were inconsistent regarding direction of effect; included studies, when taken together, had medium risk of bias. We rated the precision domain as 'imprecise' for each intervention group 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	Sertraline Paroxetine Trazodone Nortriptyline	4[*81,90,105,107,114]	Medium	Inconsistent	Direct	Imprecise	-0.61 (-1.03 to -0.19) to 0.12 (-0.31 to 0.54)	Low
Psychoactive drugs	Gabapentin Baclofen Acomprosate	3[72,101,111]	Medium	Inconsistent	Direct	Imprecise	-1.57 (-2.28 to -0.86) to -0.01 (-0.38 to 0.35)	Low
Other drugs	MEP, vardenafil, Deanxit	3[97,98,109]	Medium	Inconsistent	Direct	Imprecise	-0.68 (-1.21 to -0.16) to 0.35 (-0.26 to 0.86)	Low
Food supplement	Gingko biloba Honeybee larvae	3[76,84,103]	Medium	Inconsistent	Direct	Imprecise	-0.21 (-0.72 to 0.30) to -0.21 (-0.72 to 0.30)	Low

[*]four studies, five publications
Abbreviations: CI = confidence interval; n = number; SOE = strength of evidence; SMD = standard mean difference

Subjective loudness

Eight publications[24,77,84,98,106,109,111,114] examined loudness, primarily using subjective VAS-type scales (See Table 4). In two studies,[77,114] 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 (i.e., 15.21 vs. 5.15; p=0.014).[114] 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).[77]

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),[111] 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-poijt scale),[109] Deanxit vs. placebo (0 to 100 VAS),[98] 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).[84]

In a study[24] 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 trial[106] 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 we could only use one study in each group to make judgments about SOE. In the psychoactive drugs group, SOE is low, despite the fact that consistency across the results suggests benefits for these drugs. Risk of bias for the psychoactive 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 8 published reports presented no evidence for dose response and the risk of publication bias was high given the small sample sizes (See 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 vs. placebo	1*[90,114]	Low	Unknown (single study)	Direct	Imprecise	-0.45 (-0.95 to 0.05)	Insufficient
Psychoactive drugs	Baclofen, alprazolam acamprosate	3[24,106,111]	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[98,109]	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study[98])	Direct	Imprecise	-0.07 (-0.58 to 0.44)	Insufficient
Food supplement	Gingko biloba Zinc	2[77,84]	Medium	Unknown (single study) (Cannot calculate SMD in zinc study[77])	Direct	Imprecise	-0.91 (-1.60 to -0.22)	Insufficient

*one study, two publications
Abbreviations: CI = confidence interval; MEP = methylprednisolone injections; n = number; SOE = strength of evidence; SMD = standard mean difference

Sleep Disturbance

Three studies looked at the outcome of sleep disturbance (see Table 4). One study[105] 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, were not statistically significantly different at the end of followup. Two studies[97,98] examined sleep using the sleep disturbance subscale of the Tinnitus Questionnaire. The first[97] 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 trial[98] 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.

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 (See Table 7). In the other drug intervention group, studies of vardenafil[97] and Deanxit[98] were included in the review. However, we could not use the Deanxit study 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 vs. placebo	1[105]	Low	Unknown (single study)	Direct	Imprecise	0.31 (-0.06 to 0.67)	Insufficient
Other drugs	Vardenafil, deanxit	2[97,98]	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study[98])	Direct	Imprecise	-0.09 (-0.69 to 0.52)	Insufficient

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

Anxiety Symptoms

Three placebo-controlled studies[105,107,114] included anxiety as an outcome. Two studies (sertraline,[114] paroxetine[105]) measured anxiety with the Hamilton Anxiety Rating Scale (HAS); one study[105] also utilized the Beck Anxiety Inventory (BAI). The third study,[107] of nortriptyline (50 to 150 mg/mL for 6 weeks) versus placebo, used Sheehan's Disability Scales (SDS). The paroxetine study[105] found greater improvements in score for the placebo group on the HAS and BAI, although the differences were not statistically significant. Conversely, a study[114] 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 (i.e., 8.51 vs. 4.09; p=0.04). On the SDS,[107] the nortriptyline group showed slight improvement relative to the placebo group, but the difference was not statistically significant.

The sertraline study[114] also measured anxiety using the Comprehensive Psychopathological Rating Scale (CPRS) anxiety subscale and (in a companion paper[90]) 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 (i.e., 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).

Strength of Evidence - Anxiety Symptoms

The SOE is low 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 3 published reports presented no evidence for dose response and the risk of publication bias was high given the small sample sizes (see 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[105,107,114]	Medium	Inconsistent	Direct	Imprecise	-1.13 (-1.57 to -0.69) to 0.28 (-0.09 to 0.64)	Low

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

Depression Symptoms

Five studies considered depression, with two[105,114] utilizing more than one outcome measure. Three[105,107,114] of the five trials measured depression with the Hamilton Depression Rating Scale (HAM-D), two[98,105] with the Beck Depression Inventory (BDI), one with the CPRS depression subscale and PGWB depression subindex,[90,114] and one[76] 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)[114] and nortriptyline (difference in mean score change over followup=3.7; $p<0.05$).[107] In the sertraline study,[90,114] 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,[105] 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 crossover[98] 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 domain[76] 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 (i.e., 0.8) at week 12 favored the honeybee larvae group ($p<0.05$).

Strength of Evidence - Depression Symptoms

The SOE is low that anti-depressants[90,105,107,114] (see 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 Deanxit[98] and honeybee larvae[76]

showing depression symptoms improve relative to the inactive controls 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 reporting 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[105,107,114]	Medium	Inconsistent	Direct	Imprecise	-1.13 (-1.57 to -0.69) to 0.21 (-0.16 to 0.57)	Low
Other drugs	Deanxit	1[98]	Medium	Unknown (single study) (Cannot calculate SMD in Deanxit study[98])	Direct	Imprecise		Insufficient
Food supplement	Honeybee larvae vs. hydrogenated dextrin	1[76]	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

Global Quality-of-life

Six studies examined global QoL.[81,97,103,105,106,114] The sertraline trial[114] reported QoL results, measured using the PGWB, in a companion paper:[90] after 16 weeks of followup, the improvement in mean score compared to baseline was greater in the treated group relative to the placebo group (i.e., 20.83 vs. 2.79; p=0.001). In 4 other studies, global QoL was assessed using the Quality of Well-being Scale,[105] a 10-point VAS,[81] Short Form 36,[97] or Glasgow Health Status Inventory.[103] 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.

The acamprosate study[106] 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 low for anti-depressants versus placebo in global QoL, for the same reasons as outlined in the depressive symptoms section above (see Table 10). SOE is insufficient for acamprosate,[106] vardenafil,[97] and ginkgo biloba[103] 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 Nortriptyline	3[105,107,114]	Medium	Inconsistent	Direct	Imprecise	-0.24 (-0.60 to 0.13) to 1.06 (0.53 to 1.59)	Low
Psychoactive drugs	Acamprosate	1[106]	Medium	Unknown (single study)	Direct	Imprecise	1.53 (0.82 to 2.25)	Insufficient
Other drugs	Vardenafil	1[97]	Low	Unknown (single study)	Direct	Imprecise	-0.22 (-0.83 to 0.38)	Insufficient
Food supplement	Ginkgo biloba	1[103]	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

Adverse Effects

Adverse effects spanned a range of clinical severity, from dry or sour mouth[81,105] to confusion,[111] but generally subsided after discontinuation of treatment (see Table 11). Incidence of adverse effects varied from 3 percent[114] to 67 percent.[109] One study[106] did not report adverse effects and one trial[76] only reported that 2 persons withdrew due to 'discomfort'.

Among the anti-depressant trials, adverse effects were minimal in one trial,[114] with one sertraline participant reporting sexual dysfunction and one placebo participant reporting an unspecified problem. Eighty-eight percent of participants in the trazodone study[81] were free of adverse effects with seven reported effects in the treated group (the most serious was hypertensive crisis) and three in the placebo group (i.e., sour mouth, insomnia, sleepiness). For paroxetine,[105] eight different effects occurred during followup (i.e., 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 study[107] reported anticholinergic effects and sedation.

Turning to psychoactive drugs, nine persons withdrew from the gabapentin study[101] due to nausea (n=3), weight gain (n=2), sleep disturbance (n=2), or dizziness (n=2). These persons were assigned to the active treatment group. The baclofen trial[111] 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 alprazolam[24] 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 trial[72] 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,[109] the authors reported percentage incidences of 4 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,[97] 6 persons in the vardenafil group and 2 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),[103] 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,[84] 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,[77] two patients in the intervention group reported minor gastric disturbances. Similarly, two patients in the honeybee larvae RCT[76] dropped out due to 'discomfort' (one patient in each study group).

Table 11. Treatment emergent adverse events 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)
Anti-depressant drugs	Sertraline (SSRI antidepressant) vs. placebo[90,114]	NR	Yes	NR
	Paroxetine (SSRI antidepressant) vs. placebo[105]	22/26 (84.6%) Sexual dysfunction Tx n=17(29.8%) Pl n=4 (6.9%) p=0.001 Drowsiness Tx n=11(19.3%) Pl n=2 (3.4%) p=0.007 Dry mouth Tx n=8(14.0%) Pl 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[81]	0	NR	Sleepiness Tx n=3 (7%) Pl n=1 (2.4%)
	Nortriptyline (2nd gen tricyclic antidepressant) vs. placebo[107]	14/25 (56.0%) Anticholinergic side effects and sedation (11)	NR	NR
Psychoactive (Neurotrans-mitter) drugs	Gabapentin(GABA analogue – GABAergic) vs. placebo[101]	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[111]	8/11 (72.7%) All withdrew because of side effects (not specified)	Yes	Confusion Tx n=8 (26.7%) Pl n=0 <0.005 Dizziness Tx n=12 (40.0%) Pl n=1 (3.4%) <0.001 Drowsiness Tx n=15 (50.0%) Pl n=3 (10.3%) <0.001

Table 11. Treatment emergent adverse events reported in studies evaluating pharmacological and food supplement interventions (cont'd)

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)
Psychoactive (Neurotrans-mitter) drugs (cont'd)	Alprazolam (benzodiazepine – anxiolytic) vs. placebo[24]	2/4 (50%) Excessive drowsiness	Yes	Excessive drowsiness 7/17 (41%)
	Acamprosate vs. placebo[106]	NR	NR	NR
	Acamprosate vs. placebo[72]	9/50 (18%) 2 in Tx group and 7 in Pl 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 Pl group, including 9 participants who withdrew
Other drugs	Methylprednisolone (intratympanic injection) vs. placebo[109]	0	NR	Pain during injection Tx: 67% Pl 52% NS Burning sensation: Tx 57% Pl 17% p=0.002 Vertigo Tx 57%, Pl 38% NS Bitter taste Tx 40%, Pl 7% p=0.003
	Deanxit + clonazepam vs. placebo + clonazepam[98]	NR	NR	NR
	Vardenafil (PDE5 inhibitor) vs. placebo[97]	5/7 (71.4%)	NR	Headache Tx n=1; Pl n=2 Diarrhea Tx n=2; Pl n=0 Nasal congestion Tx n=2; Pl n=0 Prolonged penile erection Tx n=1; Pl n=0
Food supplements	Gingko biloba vs. placebo[103]	0	NR	Diarrhea Tx n=1 (3%) Pl n=2(6%) Headache Tx n=1 (3%) Pl n=1 (3%)
	Zinc vs. placebo['']	NR	Yes	Minor gastric disturbances Tx n=2 (6%); Pl n=0
	Honeybee larvae vs. hydrogenated dextrin[76]	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

Table 11. Treatment emergent adverse events reported in studies evaluating pharmacological and food supplement interventions (cont'd)

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 (cont'd)	Gingko biloba vs. placebo[84]	NR	Yes	Gastrointestinal Tx n=15; Pl n=15 Ear pressure/blocking Tx n=10 ; Pl n=4 Dizziness/nausea Tx n=6; Pl n=7 Headache Tx n=4; Pl n=4 Mouth ulcer/dryness/bad taste Tx n=3 ; Pl n=6 Worsening sleep/dreams Tx n=4 ; Pl n=3 Flushing/redness in face Tx n=1; Pl n=4 Skin problems Tx n=2 ; Pl n=3 Awareness of heartbeat Tx n=3 ; Pl n=3 Worsening hearing Tx n=1; Pl n=1 Hyperacusis Tx n=2; Pl n=2 Misc Tx n=8 ; Pl n=8

Abbreviations: AE = adverse effects; gen = generation; n = sample size; NR = not reported; NS = not significant; PDE5 = phosphodiesterase type 5; Pl= 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 (trazadone and paroxetine) and psychoactive 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 (see Table 12).

Table 12. Strength of Evidence: Studies that evaluate pharmacological and food supplement interventions compared to inactive control and report on the adverse event 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[81,105]	Low	Inconsistent	Direct	Imprecise	N/A	Insufficient
	Psychoactive Drugs (Baclofen, Alprazolam) vs. placebo	2[24,111]	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

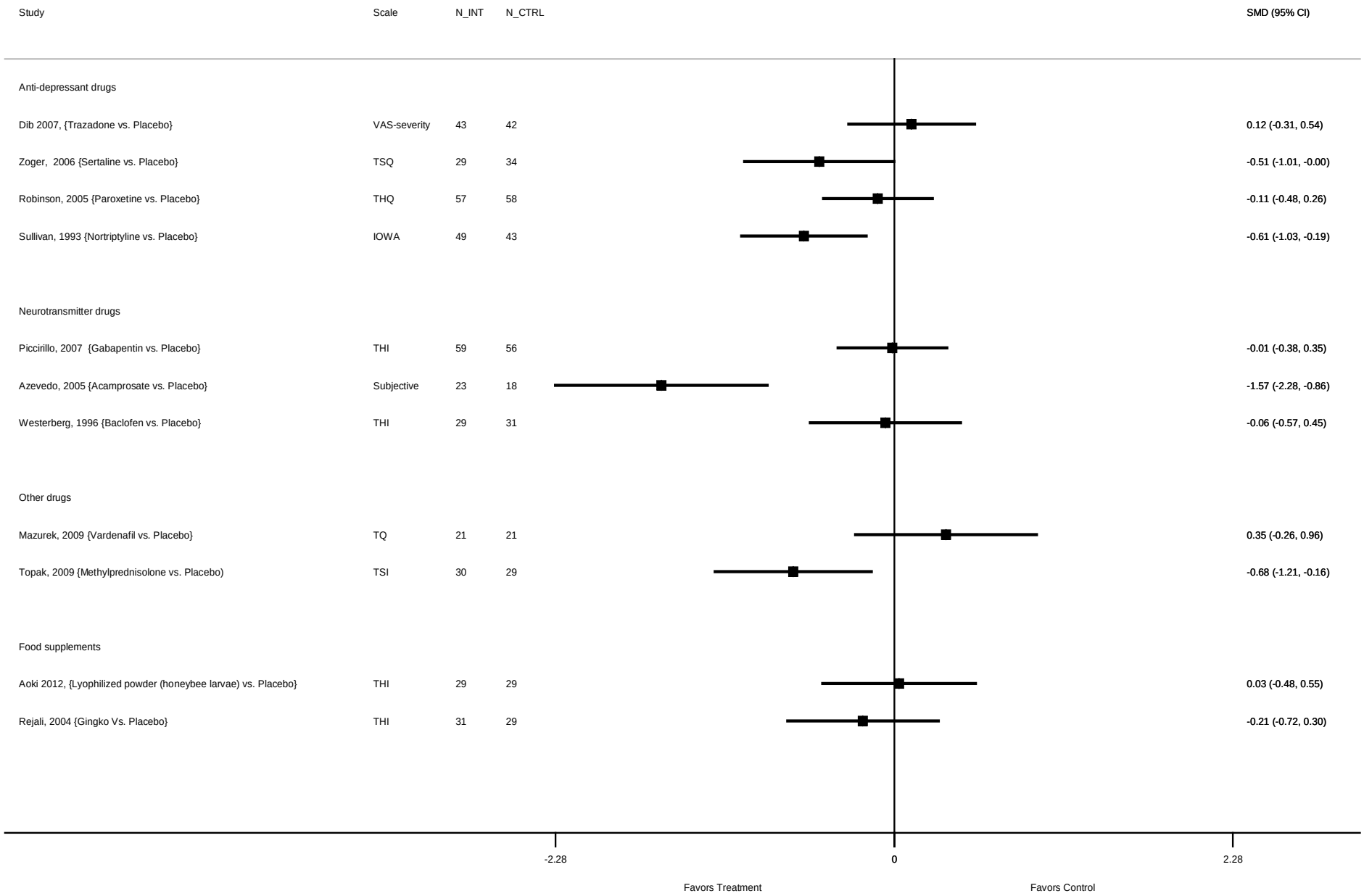


Figure 5. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report subjective loudness outcomes

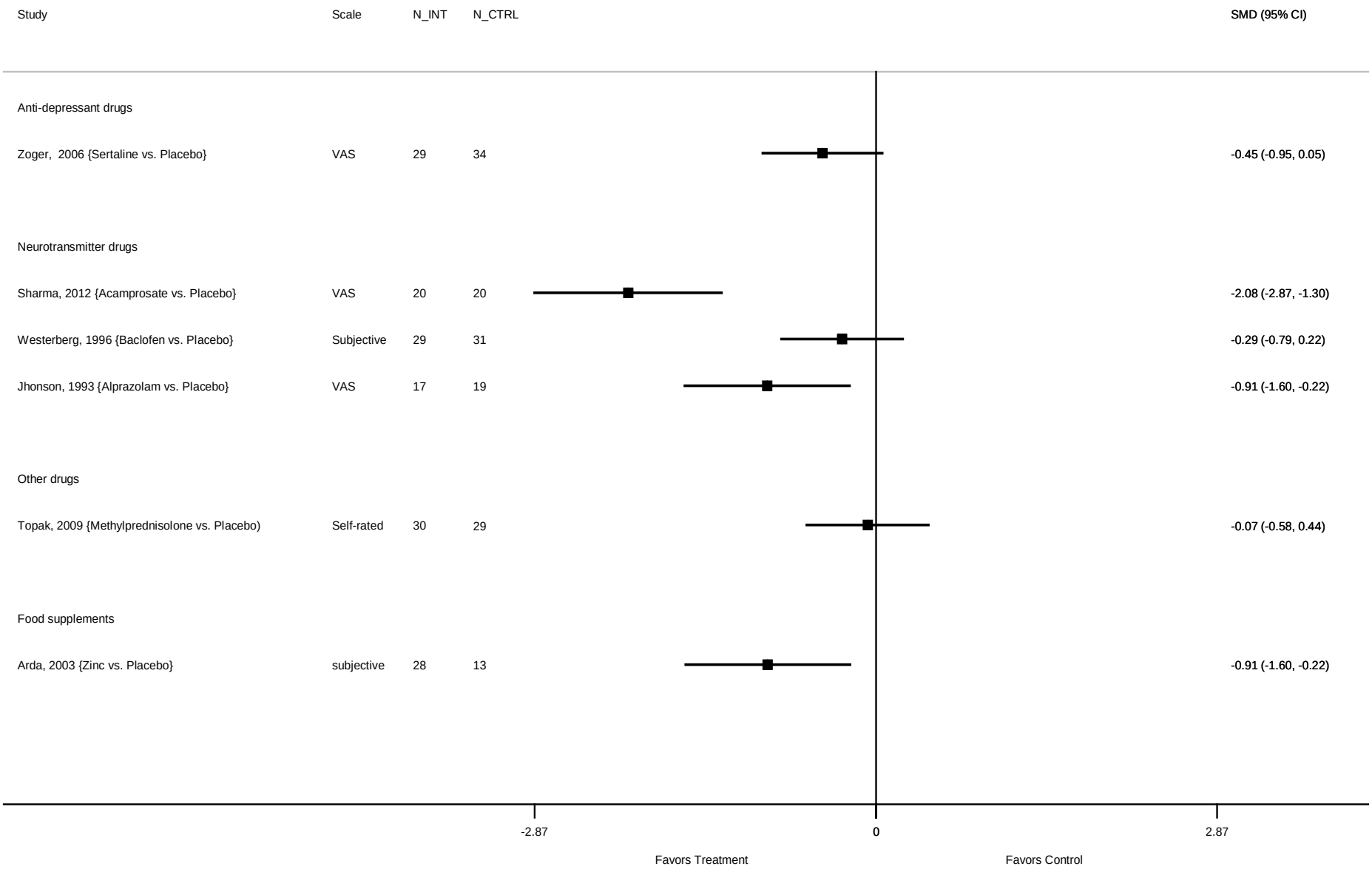


Figure 6. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report sleep disturbances outcomes

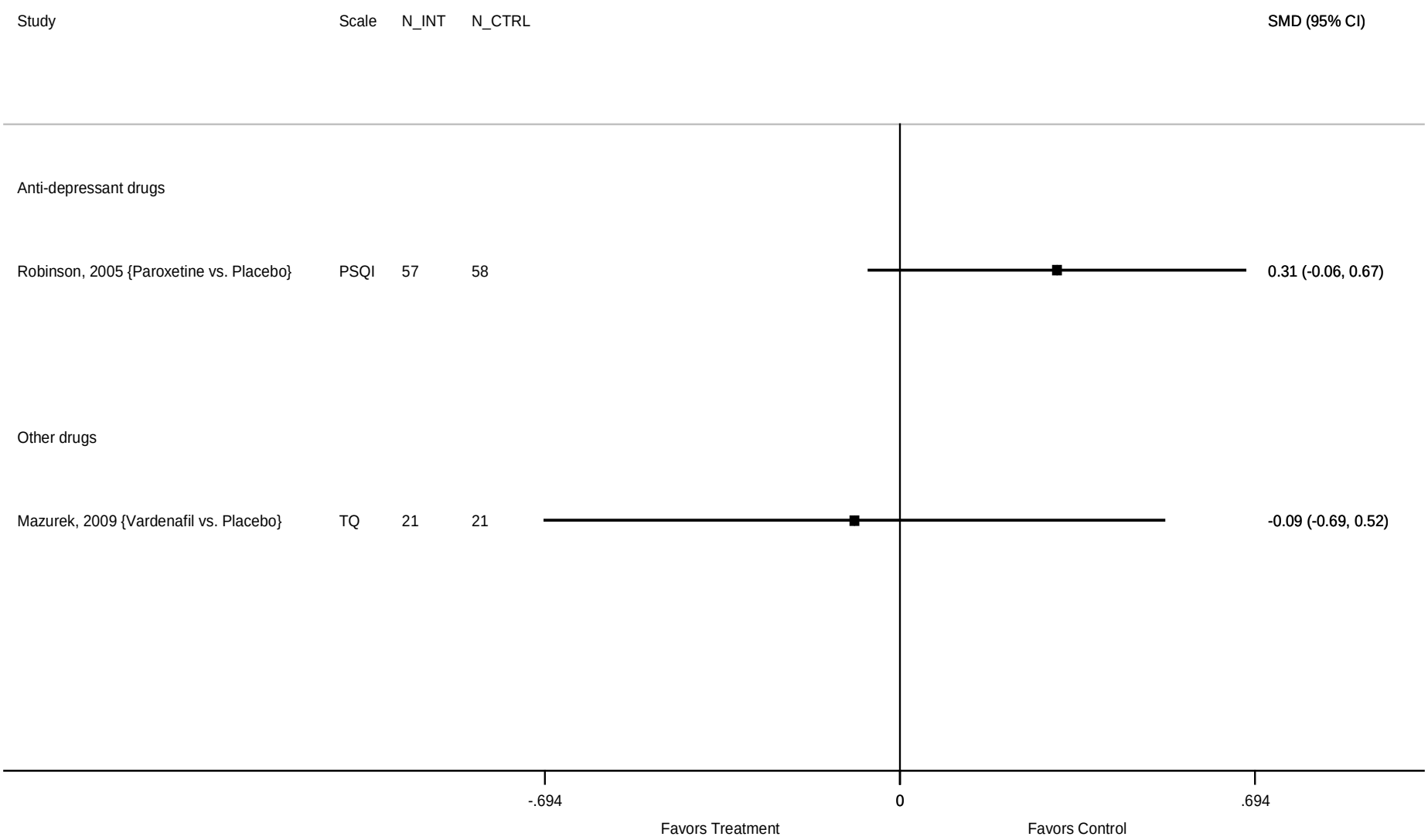


Figure 7. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report anxiety symptom outcomes

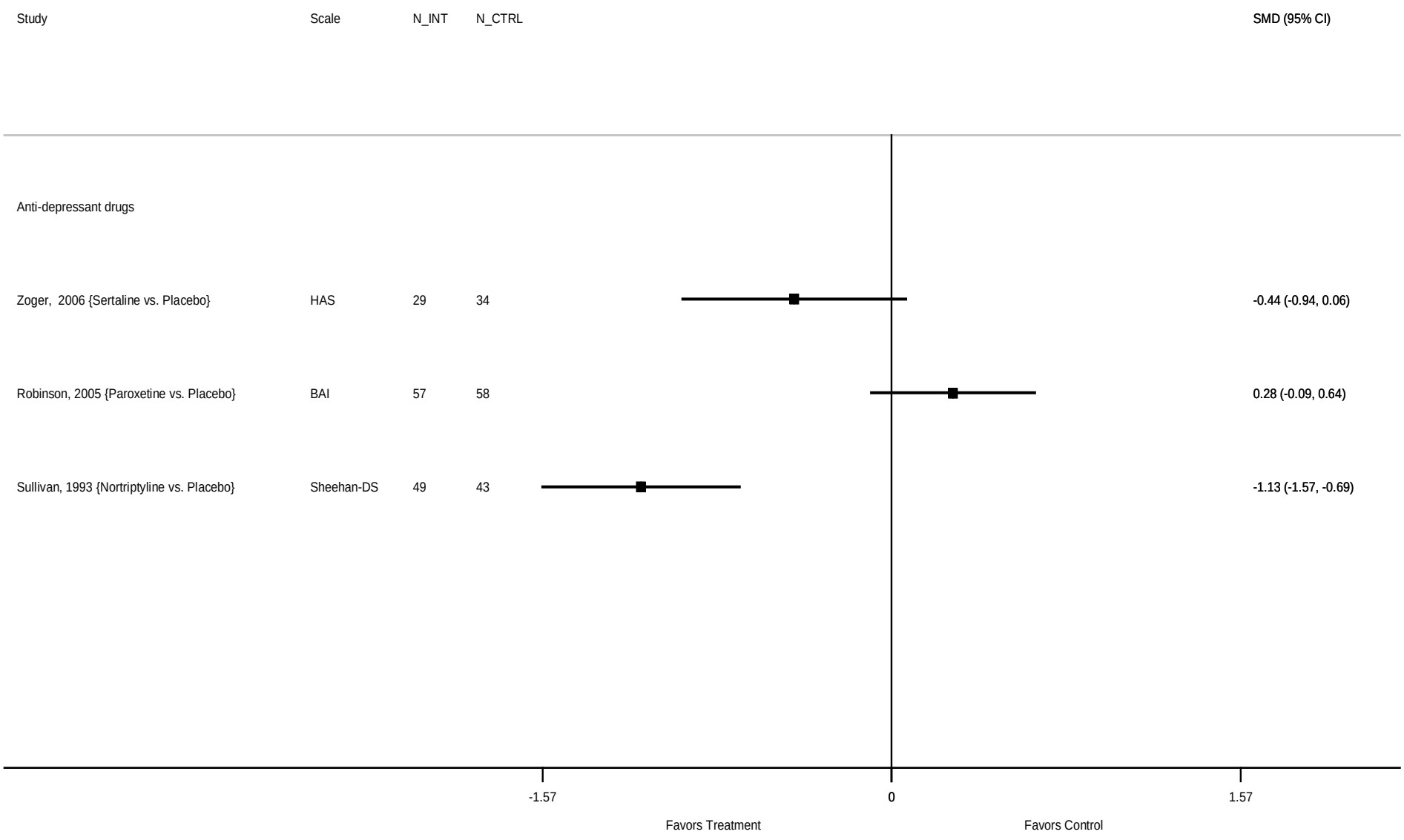


Figure 8. Studies with inactive comparators that evaluate the pharmacological and food supplement interventions and report depression symptoms outcomes

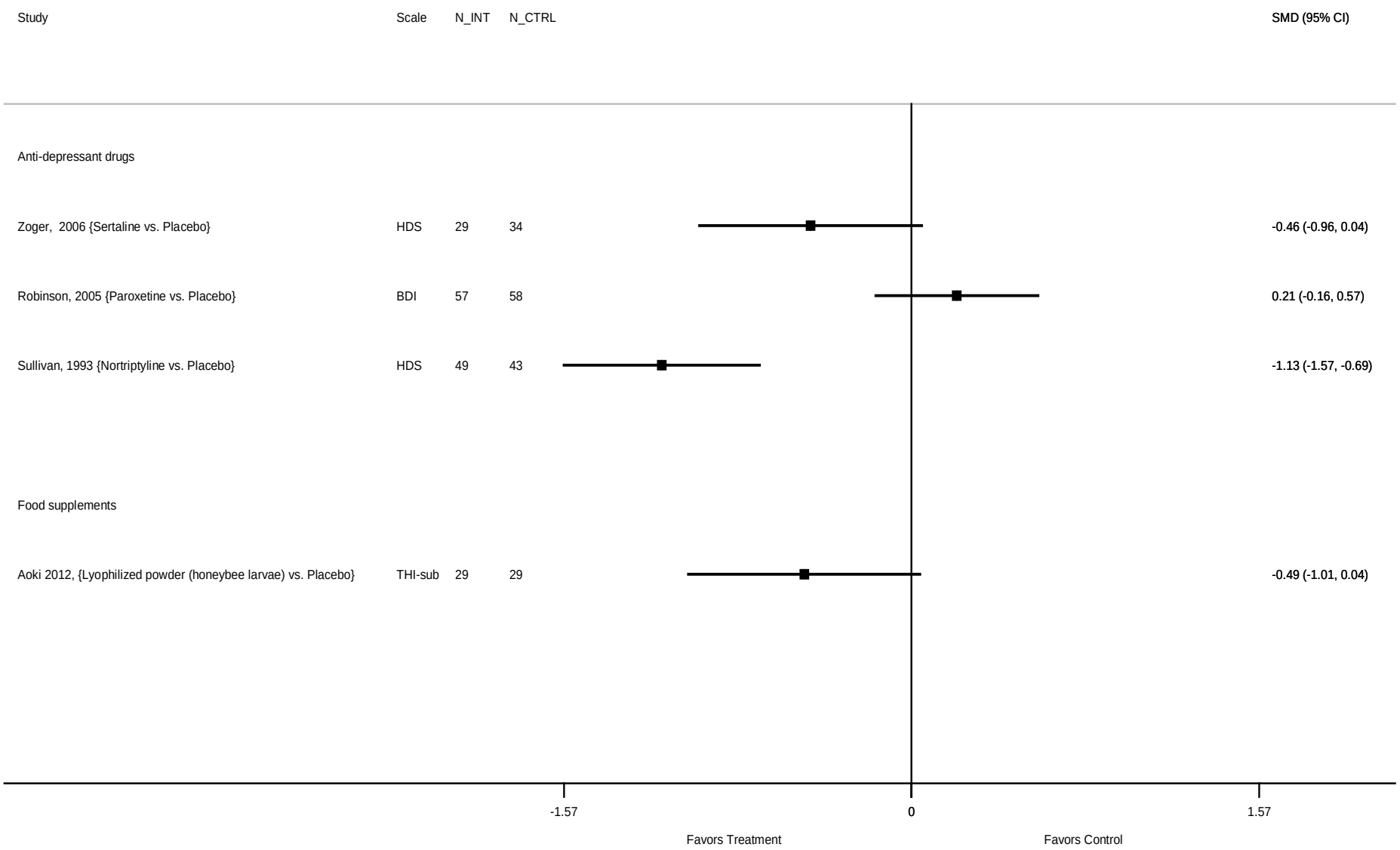
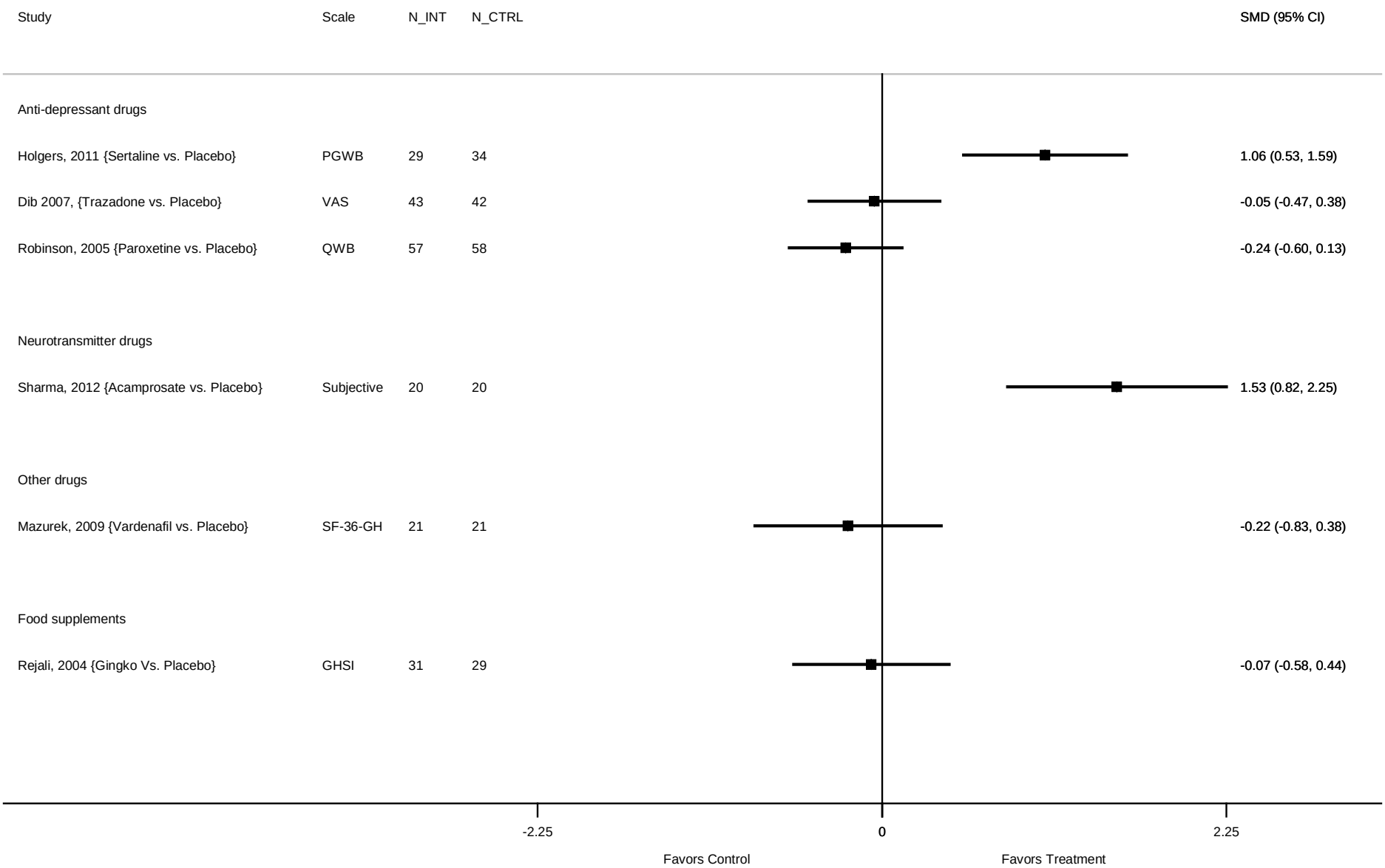


Figure 9. Studies with inactive comparators that evaluate pharmacological and food supplement interventions and report global quality of life outcomes



Medical Interventions

This grouping of studies reflects types of interventions that require the administration of the treatment generally by a clinician. They encompass a variety of modalities, including, repetitive transcranial magnetic stimulation (rTMS), acoustic coordinated reset neuromodulation (ACRN), low level laser therapy (LLLT), and acupuncture.

Characteristics of Included Studies

Eleven studies were included for medical interventions in KQ2. Six[73,79,85,94,96,102] of these evaluated repetitive transcranial magnetic stimulation (rTMS) or electromagnetic stimulation, three evaluated low level laser therapy (LLLT)[31,80,99] and one each evaluating acupuncture[110] and acoustic coordination reset neuromodulation (ACRN) therapy.[108] See Appendix D 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 disease[31] or tinnitus that was treatment resistant for one year).[110]

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,[80,96] 6 months,[73,85,108] 1 year,[110] or less than 5 years.[102] 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[73,79] and had symptoms that had not resolved following pharmacological interventions after 3 months[73] or any following any other type of treatment.[79] 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,[94] disabling chronic,[99] and chronic.[108] Other papers enrolled patients with treatment resistant tinnitus,[79,110] and three did not report on severity of tinnitus at enrollment.[31,96,102] Some studies included a pre-study assessment by an otolaryngologist (ENT),[79,80] and audiologist or audiology tests.[73,85,94,99]

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,[85] less than 5 years,[102] and 6 months to 20 years.[79] One study provided only mean duration of tinnitus (11.7 and 10.7 years).[94] Two studies did not report duration of symptoms of included subjects.[73,96]

The study evaluating ACRN[108] 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[31,99] and 6 months to 45 years.[80] The acupuncture study[110] reported only the average duration (from 7.4 and 9.4 years).

Interventions and Role of Device Manufacturers

Repetative Transcranial Magnetic Stimulation (rTMS) and Electromagnetic Stimulation.

Five studies focused on rTMS[73,79,94,96,102] and one on high-frequency pulsed electromagnetic energy.[85] Table 13 shows the specifics of the rTMS and electromagnetic stimulation devices,

dose and placement on the head. One study[85] 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[73,94] used additional devices (stereotaxy and MRI) to locate the cortical areas of interest (see Table Medical 1). The electromagnetic stimulation parameters markedly varied with respect to number of session (5 sessions over two weeks)[73] to 20 consecutive sessions over 4 weeks.[102] Similarly, the dose of electromagnetic stimulation varied across studies from 1500 stimulations at 1 Hz[73] to 900 bursts at 5 Hz.[102]

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,[85] 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 µs 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 mnth. 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,[73] 2010	Device: Magstim SuperRapid; (The Magstim Company Ltd., Whitland, UK). Coil: Figure-eight-shaped coil	(rTMS) 1500 stimulations per session and this occurred over 2 intervals within a session at 1 Hz. In total 5 sessions over 2 weeks.	Navigation of the coil on the surface of the skull Frameless neuro-navigation system (Magstim Co. Ltd, Whiteland, UK) over the auditory cortex (Brodman 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. Sham rTMS: coil was tilted 45 degrees away from skull with only one wing touching the skull

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

Study	Device	Dose and Duration	Information about the location and method of treatment application as specified within the studies.
Marcondes,[96] 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 tempoparietal 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,[79] 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.
Plewnia,[102] 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 inhibitatory effects. Patients received daily cTBS for 4 weeks (20 sessions).	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 Tempoparietal 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 _ 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. For adequate masking of the patients, sham stimulation was performed as per cTBS but behind the mastoid.

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

Study	Device	Dose and Duration	Information about the location and method of treatment application as specified within the studies.
Langguth,[94] 2008	Medtronic (90 mm outer diameter, Medtronic, Minneapolis, MN, USA) Figure 8 coil	The study aimed o investigate whether priming stimulation enhances the efficacy of low-frequency rTMS Intervention: Priming protocol (960 stimuli; 6 Hz) preceded rTMS (1040 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: (2000 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 study[108] 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 (left brain), 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 optimize 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 one 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 ear phones; 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 had a role in the initial assessment of tinnitus frequency). 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)[31,99] relative to sham laser and one study used LLLT in combination with counseling relative to sham LLLT and counseling.[80] 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 study[99] used gallium-aluminium-arsenade (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[31,80] used a similar laser device (see website for this device - http://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 study[31] used the TinniTool (Adisma ©) and a second study[80] 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 study[31] 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 study[80] 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 study[80] 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 used a multi-modal approach and combined tinnitus retraining therapy principles and psychosomatic approaches (both hypnotic and relation techniques) over the 10 sessions.

Acupuncture

One study reviewed the effects of Chinese acupuncture relative to sham acupuncture.[110] Treatments were given over two months where subjects received 3 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 in the included in the studies. Description of the sham interventions are described in the interventions section.

Table 14. Medical interventions and outcomes

Medical Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
RTMS		**INACTIVE COMPARATOR**							
	1	rTMS vs. sham Anders,[73] 2012						THI*, TQ-modified, VAS	yes
	2	rTMS vs. sham Marcondes,[96] 2010						THI	none
	3	rTMS vs. sham, Chung,[79] 2012				VAS		THI* TQ	none
	4	rTMS (cTBS) secondary auditory cortex vs. sham, Plewnia,[102] 2012						TQ	yes
		rTMS (cTBS) temperoparietal cortex vs. sham, Plewnia,[102] 2012						TQ	yes
	5	High-Frequency Pulsed Electromagnetic Energy vs. sham Ghossaini,[85] 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,[94] 2007						TQ	none
	2	rTMS (cTBS) secondary auditory cortex vs. rTMS (cTBS) temperoparietal cortex, Plewnia,[102] 2012						TQ	yes
Acupuncture		**INACTIVE COMPARATOR**							
	1	Acupuncture vs. sham Vilholm,[110] 1998				VAS		VAS-Ann*, VAS-Awr	NR
Laser		**INACTIVE COMPARATOR**							
	1	Laser Therapy vs. sham Mirz,[99] 1999		STAI	BDI	VAS		THI*, VAS-Ann, VAS-Att	none
	2	Laser Therapy vs. sham Teggi,[31] 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,[80] 2008						THI	NR

Table 14. Medical interventions and outcomes (cont'd)

Medical Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
Neuro-modulation		**INACTIVE COMPARATOR**							
	1	ACRN G1 vs. placebo Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G2 vs. placebo Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G3 vs. placebo Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G4 vs. placebo Tass,[108] 2012				VAS		TQ* VAS	yes
		Head to Head							
	1	ACRN G1 vs. G2, Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G2 vs. G3, Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G3 vs. G4, Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G1 vs. G3, Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G1 vs. G4, Tass,[108] 2012				VAS		TQ* VAS	yes
		ACRN G2 vs. G4, Tass,[108] 2012				VAS		TQ* VAS	yes

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

Outcomes

Most studies reported data on more than one outcome (see table 14, see also Appendix D). 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	1. THI (Tinnitus Handicap Inventory)[31,73,79,80,85,96,99] 2. TQ (Tinnitus Questionnaire)[73,79,94,102,108] 3. VAS (Visual Analogue Scale)[73,99,108,110] 4. TMR (Tinnitus Magnitude Rating)[85]
Sleep Disturbance	No study evaluated this outcome
Anxiety Symptoms	1. STAI (State-Trait Anxiety Inventory)[99]
Depression Symptoms	1. BDI (Beck Depression Inventory)[99]
Subjective loudness	1. VAS (Visual Analogue Scale)[6,14,24,31,79,91,99,108,110,114]
Global Quality of Life	No study evaluated this outcome

Setting

The research settings were in departments of Otolaryngology/Otorhinolaryngology,[73,80,96,99] Audiology,[110] Otorhinolaryngology and Psychiatry,[102] Psychiatry,[94] and Ear, nose and throat.[31] Other settings included tinnitus clinics[108] and a university medical hospital.[79] One paper did not report on the research setting.[85]

Country

The studies were carried out in seven different countries: the United States;[85] China;[79] Germany;[94,102,108] Denmark;[99,110] Italy;[31,80] Spain;[96] and the Czech Republic.[73] See Appendix D. Table B.

Sources of Funding

Sources of funding were not reported in six studies.[31,80,96,99,102,110] One study reported industry funding,[108] and one received a loan of the equipment being tested.[85] The remaining studies received funding from research councils, foundations, and government departments and non-profit associations.[73,79,94]

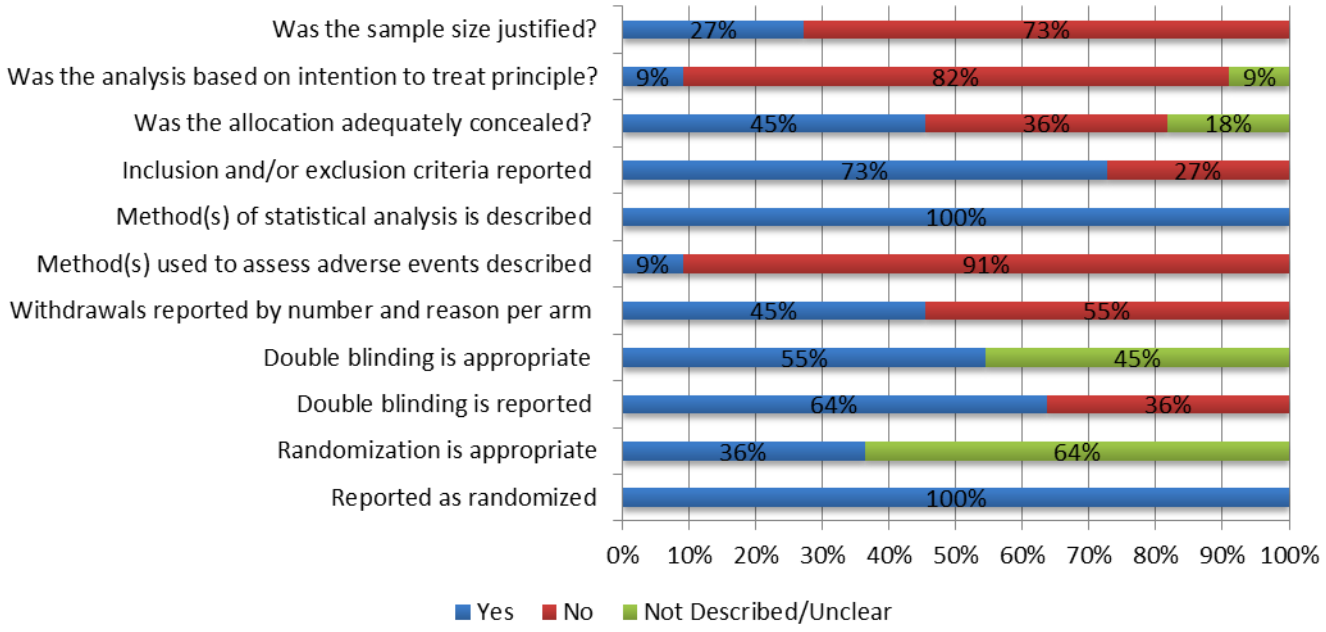
Risk of Bias for Medical Interventions

The risk of bias in the eleven studies evaluating medical interventions was generally fair risk of bias (n=9 fair,[31,73,80,85,94,96,99,108,110] n=1 poor,[79] n=1 good[102]). All authors reported their studies as randomized, with appropriate randomization in 36 percent (n= 4) of articles.[31,94,102,108] Method of randomization was not described in seven papers (64%).[73,79,80,85,96,99,110] Some articles reported using double-blinding techniques,[31,73,80,85,96,99,110] and in all but one case[110] it was deemed appropriate. Seventy three percent of articles (n=8) reported the inclusion/exclusion criteria,[73,79,80,94,96,102,108,110] 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%),[79,85,96,99,108,110] no description of methods to assess adverse effects (n=4, 36%),[79,94,108,110] inadequate concealment of allocation (n=10, 91%),[31,73,79,80,85,94,96,99,108,110] analysis not based on

intention-to-treat principle (n=9, 82%),[31,73,79,85,94,96,99,108,110] and inadequate justification of sample size (n=8, 73%).[31,73,79,80,85,96,99,110]

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[73,79,96,102] or electromagnetic stimulation[85] relative to an inactive control (see also Table 15). Most of these studies used the TQ or the THQ to evaluate tinnitus-specific QoL. Two studies[73,96] at high risk of bias investigated low frequency (1 Hertz) 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 the week 6 (relative to week 2) on the THI.[73] There were statistically significantly reductions relative to baseline in the active treatment groups at 26 weeks[73] and six months.[96] However, active treatment appeared not to confer any further reductions in score after 6 weeks[73] or at 1 month.[96] 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 studies[96] selected subjects with lower THI scores at baseline relative to other studies, suggesting that they had less severe tinnitus.

Two studies[79,102] investigated higher frequency (5 Hertz) rTMS relative to sham stimulation and measured the outcome using the THI. One of these studies[79] was at high risk of bias, and administered treatment for 10 consecutive days and showed significant differences on TQ and

THI scores 1 week post treatment ($p < 0.01$) but not at 1 month. The second study[102] 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 study[85] at high risk of bias examined high-frequency (27.2 MHz) electromagnetic energy using the THI as the outcome measure. The high frequency study[85] 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).[108] However, none showed a significant effect favoring treatment relative to placebo (see 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[31,99] evaluated LLLT compared to an inactive control, and one study[80] 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.[80,99,110] All studies showed no statistical differences between the treatment and comparator groups using the THI. It is noteworthy that one study[99] used a markedly different form of LLLT relative to the other two studies[31,80] which used a self-administered applied for a minimum of 3 months. One study[99] evaluated 100 mm VAS for annoyance and found no between-group differences ($p=0.81$); similarly, a VAS for attention to symptoms was evaluated no statistical differences were shown ($p=0.52$) immediately post treatment (one month).

Acupuncture

A single trial[110] compared traditional Chinese acupuncture to sham acupuncture over 2 months of treatment and evaluated up to four months of followup. Results on an unspecified VAS were not statistically significantly different at the 5% level for 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 events were not systematically evaluated and none were reported.

Strength of Evidence - Tinnitus-specific Quality of Life

For the rTMS studies, the small sample sizes, lack of power calculations, and wide confidence intervals, contributed to our rating of imprecise. We judged the direction of effect to be inconsistent across studies; high frequency rTMS studies[79,102] showed differing directions of effect (statistically significant differences favoring treatment or no difference between groups) and low frequency rTMS studies[73,96] favoring treatment but were not statistically significant. With respect to the magnitude of the treatment effects, we found studies were also inconsistent in that effect sizes varied from 0.02 to -1.23. With respect to risk of bias, the studies were categorized as high risk of bias (only one study[102] achieving 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 strength of evidence (SOE) for rTMS for the outcome of tinnitus related quality of life is rated as insufficient even though 4 studies were eligible for review (see Table 16). The study evaluating high frequency electromagnetic stimulation[85] is considered sufficiently different to traditional rTMS that we placed it in its own category for SOE.

For LLLT studies, both studies were rated as high risk of bias. One study showed no difference between groups and another favored control but was not statistically significant; the effect sizes varied from -0.0 to 0.33 and were deemed as inconsistent (see Table 16). Although the confidence intervals overlapped substantially, the small sample sizes, 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. Risk of publication bias is high given the small sample sizes of the study and limited to single publications.

When considering the high frequency electromagnetic stimulation, ACRN and acupuncture intervention studies, we deemed the evidence as insufficient given the high risk of bias and small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes of the study and few number of eligible studies.

Table 16. Strength of evidence for medical interventions in the treatment of tinnitus for the outcome Tinnitus-Specific QoL 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[73,79,96,102]	High	Inconsistent	Direct	Imprecise	-1.23 (-2.16,-0.30) to -0.02 (-0.67, 0.72)	Insufficient
Hi-frequency electromag-netic energy vs. sham	N/A	1[85]	High	Unknown	Direct	Imprecise	-0.13 (-0.86, 0.60)	Insufficient
ACRN vs. sham	N/A	1[108]	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[31,99]	High	Inconsistent	Direct	Imprecise	-0.00 (-0.54, 0.53) to 0.33 (-0.29, 0.94)	Insufficient
Acupuncture vs. placebo	N/A	1[110]	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,[31,79,99,108,110] (summary risk of bias score did not exceed 7 from 12) examined loudness as an outcome in persons given medical interventions including LLLT and acupuncture (see 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 D. Table B for full study details for this outcome).

One study[108] evaluated the impact of ACRN on subjective loudness (VAS) measured after 12 weeks of treatment and showed some differences (G1, 24 point decrease on 100 mm VAS) relative to placebo (G5, 9 point decrease) with the exception of the G1 group which favored treatment (p=0.07).

Two studies involved LLLT versus sham LLLT, with one article[31] finding less loudness (measured on a 10 cm VAS) in the treated group after 3 months of patient-administered daily treatment (mean difference=2.91 favoring treatment; p=0.01). In the other LLLT study,[99] 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,[110] 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

Table 17 shows the SOE for the outcome of subjective loudness. All the studies measuring this outcome consistently showed no statistical differences between treatment and inactive control groups; however the studies had small sample sizes and it is not clear if this is a factor in the results and as such the studies are considered imprecise. Both LLLT studies favored control but were not statistically significant; the effect sizes were generally small. The study evaluating ACRN consistently favored treatment but only one does was statistically significant

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

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[108]	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[31,99]	High	Consistent	Direct	Imprecise	0.23 (-0.34, 0.80) to 13 (-0.40, 0.66)	Insufficient
Acupuncture vs. placebo	N/A	1[110]	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 bias[99] evaluated active versus sham LLLT (Ga-Al-As, diode laser) administered by a clinician (see Table 15). The State Trait Anxiety Inventory (STAI) was evaluated at baseline and 1 month following treatment. For laser,[99] mean score on the STAI was lower in the LLLT group yet not statistically significant (p=0.74).

Strength of Evidence - Anxiety Symptoms

The SOE for this single study which used LLLT and reported impact on anxiety symptoms (using the STAI) was rated as insufficient (see Table 18). The study was at high risk of bias, small sample size, and a wide confidence interval (imprecise).

Table 18. Strength of evidence by medical interventions in the treatment of tinnitus for the outcome 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[99]	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 bias[99] evaluated depressive symptoms following the use of LLLT (Ga-Al-As, diode laser) administered by a clinician (see Table 15). 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 SOE for this single study which used LLLT and reported impact on depression symptoms (using the STAI) was rated as insufficient (see Table 19). The study was at high risk of bias, small sample size, and a wide confidence interval (imprecise).

Table 19. Strength of evidence by medical interventions in the treatment of tinnitus for the outcome 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[99]	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 (see Table 15).

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 study[102] 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.

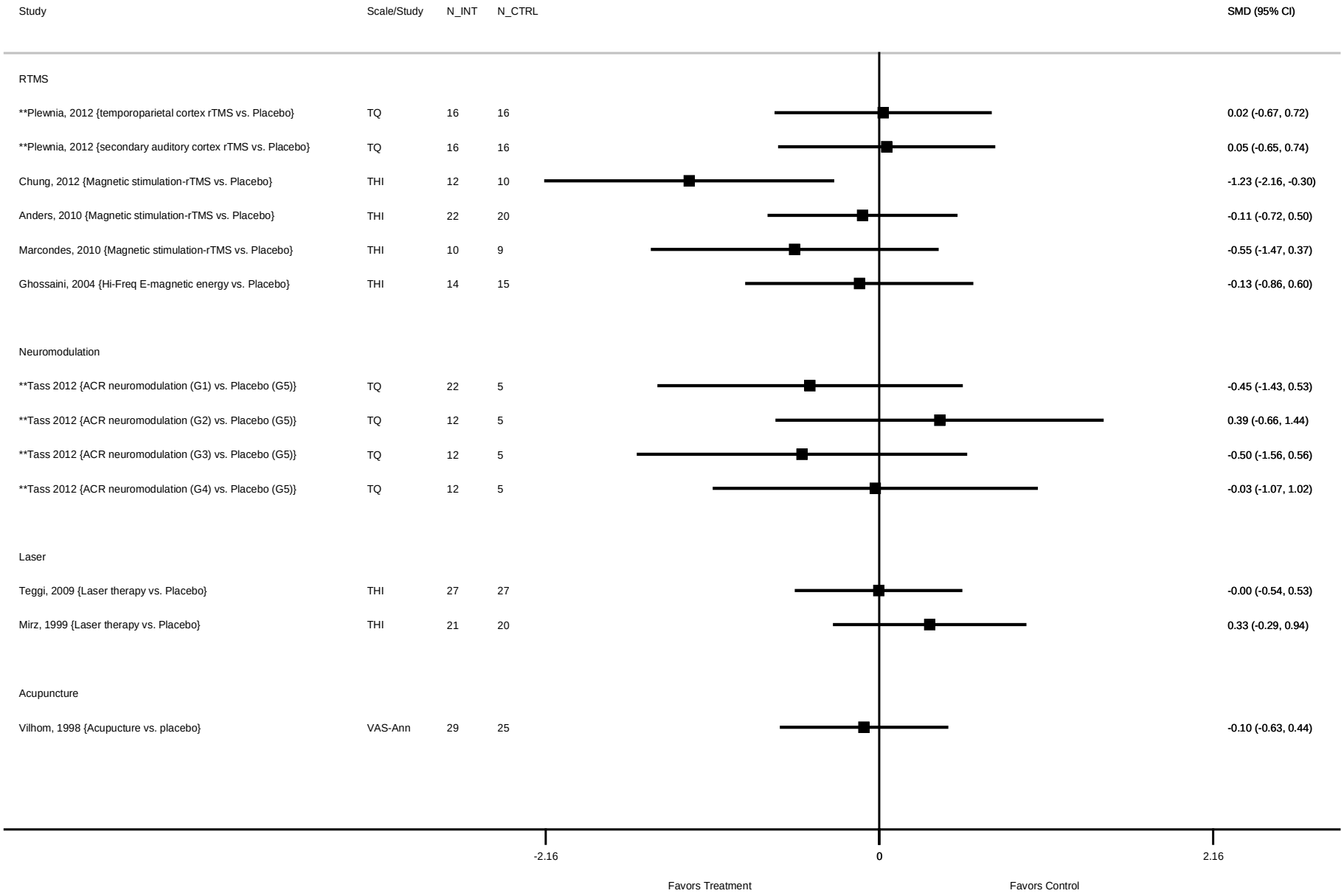
Table 20. Description of reported adverse effects in the medical intervention studies

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[73]	0	NR	Worsening of Tinnitus symptoms (n=2)
	rTMS vs. sham[96]	0	NR	All patients tolerated rTMS without relevant side effects
	rTMS vs. sham[79]	0	NR	Transient jaw soreness (n=5) Temporary orbital twitching (n=3) Facial myalgia (n=1)
	rTMS vs. sham[102]	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[94]	0	NR	Treatment was well tolerated. No serious A/E were observed.
	High-Frequency Pulsed Electromagnetic Energy vs. sham[85]	0	NR	Worsening of Tinnitus symptoms Tx n=4 (26.6%); Pl n=5 (35.7%)
ACRN	ACRN vs. sham[108]	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[99]	0	NR	Some experienced warmth inside the ear canal No serious untoward AE noticed
	LLLT vs. sham[31]	2/4 (50%)	NR	Increase in tinnitus loudness n=2
	Laser + counseling vs. sham + counseling[80]	0	NR	NR
Acupuncture	Acupuncture vs. sham[110]	0	NR	NR

* All patients underwent a standard otolaryngologicalphysical examination as a safety assessment. At every treatment visit, tolerability and safety was assessed by spontaneous adverse event 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.

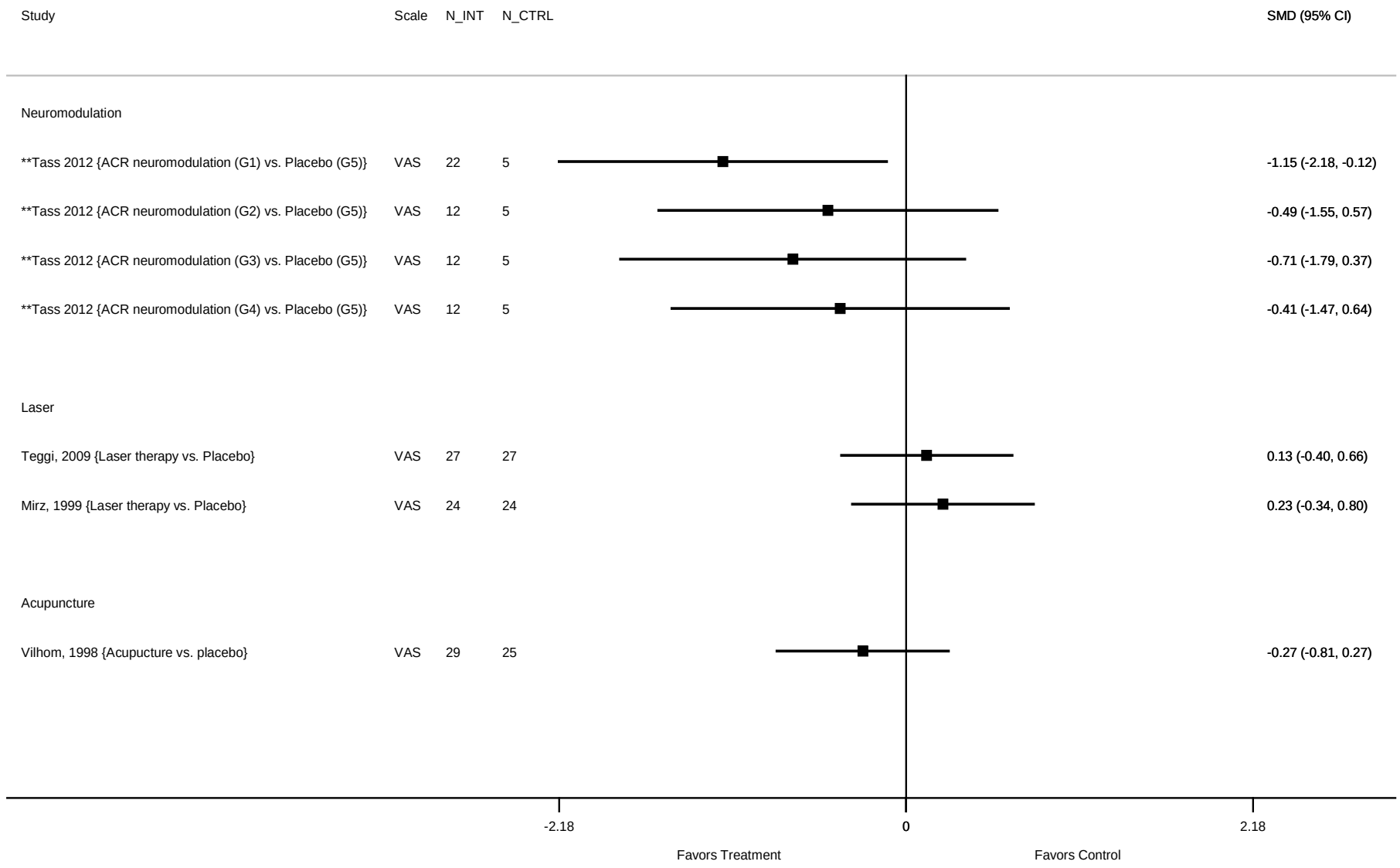
Abbreviations: ACRN = acoustic coordinate reset neuromodulationl; AE = adverse event(s); CBT = cognitive behavioral training; CI = confidence interval;LLLT = low level laser treatment; LTE = longterm evaluation; med/surg = medical/surgical; n = sample size; NR = not reported; NS = not significant; Pl = 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

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



** Represent studies with multiple intervention groups

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



** Represent studies wih multiple intervention groups

Sound Technology Interventions

Characteristics of Included Studies

Five publications were included for KQ2 and were classified into the sound treatment/technology intervention category (see Table 21).[46,82,83,89,100] Two articles reported on the same results[82,83] and only the later[83] 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).[89] See Appendix D 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.[89] In other papers, the majority of the participants were identified as having tinnitus for 11 years,[46] and 69.5 months.[100] One study did not report on the duration of tinnitus prior to the intervention.[83]

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 tinnitus[46] while one included individuals with chronic tinnitus.[89]Two articles did not report on the severity of tinnitus.[83,100] The presumed etiologies of tinnitus were described as hearing loss,[89] and bilateral hearing loss.[100] Presumed etiology was not reported in two studies.[46,83]Audiological factors at study enrollment included decreased sound tolerance,[46] 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.[100]Two articles did not report on audiological factors at enrollment.[83,89]

Head to Head Interventions

All four studies[46,83,89,100] categorized under the sound treatments/technology category (Table 4 and Appendix D. Table C) focused on head to head comparison including: hearing aids versus sound generators;[100] one stage intermittent perception plus two stage complete covering of perception initially, then intermittent;[46] information only, information plus relaxation training, information plus long-term low level white noise (LTWN), information plus relaxation training plus LTWN;[83] and cognitive behavioral therapy (CBT) with noise generator (NG), CBT alone, tinnitus education (TE) plus NG, and TE with no NG.[89]

Table 21. Sound treatment/technologies – interventions and outcomes

Sound Treat Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
		HEAD TO HEAD							
	1	Hearing aids vs. SG Parazzini,[100] 2011				subjective	VAS	THI	NR
	2	Neuromonics Tinnitus Treatment – 2nd study One-stage: Intermittent perception Two-stage: complete covering of perception initially, then intermittent Davis,[46] 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,[82,83] 1997,1999				VAS	DSP (total stress)	TRQ, VAS VAS (coping), change in awareness	NR
	4	CBT with NG CBT alone Hiller,[89] 2004 STUDY A		WI		VAS		TQ, T-cog	NR
	5	TE (tinnitus education) plus NG TE no NG Hiller,[89] 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; THI = Tinnitus Handicap Inventory; TQ = Tinnitus Questionnaire; VAS = visual analogue scale; WI = Whiteley Index

Outcomes

Most studies reported data on more than one outcome (Tables 21, also Appendix D). The outcome measurement instruments used varied for the same outcomes (Table 5). For example, four different instruments were used to measure the outcome of tinnitus-specific quality of life. 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.' A new outcome, 'tinnitus-specific quality of life,' was added, and combined the categories 'discomfort' and 'severity.' All but one study examined outcomes using validated measurement instruments within this domain.[100]

Table 22. Outcome measurements used sound technology

Outcome	Outcome Measurement Used
Anxiety Symptoms	WI (Whiteley Index)[89]
Subjective loudness	VAS (Visual Analogue Scale)[46,83,89] Subjective[100]
Global Quality of Life	VAS (Visual Analogue Scale)[100] DSP(The Derogates Stress Profile)[83] SCL-90R (Symptom Checklist, general psychopathology[89]
Tinnitus-Specific Quality of Life	TRQ (The Tinnitus Reaction Questionnaire)[46,83] TQ (Tinnitus Questionnaire)[89] VAS (Visual Analogue Scale)[46,83,89] TRSS (Tinnitus-Related Self-Statements Scale)[14]

Setting

The research settings were a tinnitus clinic,[100] a university hearing clinic,[83] and an outpatient department.[89] One paper did not report the setting.[46]

Country

The studies were carried out in Australia[46,83] the United States and Italy,[100] and Germany.[89]

Sources of Funding

Sources of funding included the Australian Commonwealth Government via a Biotechnology Innovation Fund,[46] grants from a Tinnitus Research Initiative,[100] and financial support from the German Tinnitus Association.[89] One paper did not reveal the source of funding.[83]

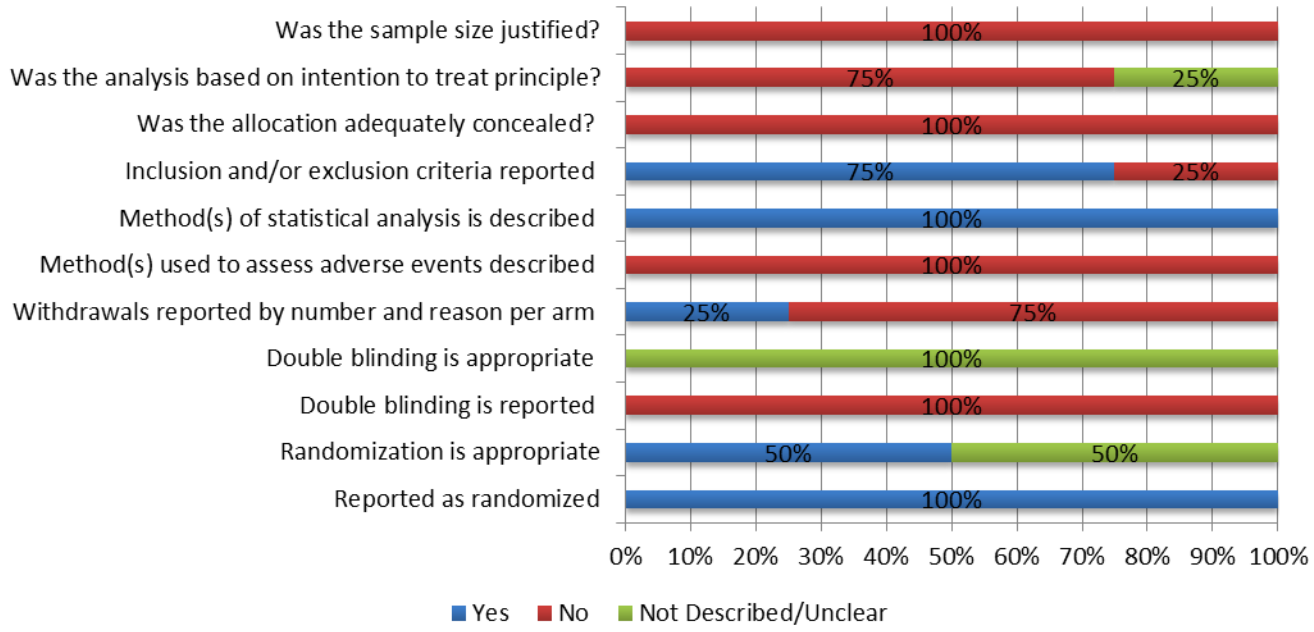
Risk of Bias for Sound Technologies

The risk of bias in the four studies evaluating sound treatments/technology interventions was mixed (n=3 fair; n=1 poor).[46,83,89,100] All authors reported their studies as randomized, with appropriate randomization in 50 percent (n= 2) of articles[46,100] and not described in two (50%).[83,89] All articles did not involve double-blinding due to the nature of the interventions. Seventy five percent of articles (n=3) reported the inclusion/exclusion criteria,[46,89,100] 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%),[46,83,100] no description of methods to assess adverse effects (n=4, 100%),[46,83,89,100]

inadequate concealment of allocation (n=4, 100%),[46,83,89,100] analysis not based on intention-to-treat principle (n=3, 75%),[83,89,100] and inadequate justification of sample size (n=4, 100%).[46,83,89,100]

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,[46,83] the TQ and VAS,[89] and the THI.[100] 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.[100] 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.[46] 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.[83] No significant effect of intervention was found on the TQ or the T-Cog (Tinnitus Cognition Scale) in a study[89] investigating whether use of a low level white-noise generator (NG) would enhance the effects of CBT (a full 10-session CBT with or without NG was delivered to those with severe tinnitus-related distress) or tinnitus education (TE; a 4-session TE intervention with or without NG was delivered to those with moderate tinnitus-related distress), with the degree of tinnitus-related stress determined using the STI (however, participants who preferred the shorter or longer intervention were also permitted to attend the one of their choice).

Overall, significant benefits of treatment in terms of tinnitus-specific quality of life 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[83,89,100] evaluated the effects of intervention on the subjective loudness of the tinnitus.[83,89,100] Significant reductions in subjective loudness were reported in one study[100] 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.[83] 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.[89]

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 study[89] evaluated the effects of intervention on anxiety. In one study[89] 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.[89]

Depression

Only one study reported the effects of the interventions on depressive symptoms. No significant effect of CBT treatment either with or without noise generators (NG) was found when the SCL-90R was used to measure depression,[89] 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,[83,89,100] 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.[100] 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.[83] The SCL-90R (Positive Symptom Distress Index; PSDI) and the Dysfunctional Analysis Questionnaire (DAQ) were used to measure psychopathology and psychosocial functioning, respectively,[89] 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; as such the each study could be assessed individually. 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. In this regard all the studies evaluating sound technologies (relative to different active comparators) were considered to be at high risk of bias and consistency is unknown. The very small sample sizes within the studies is a factor considering these studies as imprecise. Overall, there is insufficient information to judge the SOE for the head to head studies evaluating sound technologies.

Psychological and Behavioral Interventions

Characteristics of Included Studies

A total of 19 RCT articles[7,13,14,52,54,71,74,75,78,86-88,91-93,95,104,112,113] evaluated interventions in the psychological and behavioral domain (see Table 23, also Appendix D. Table D). 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.

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,[88] individuals from various industrial organizations,[71] and older adults.[75]

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.[78] In other studies tinnitus had to have been bothersome for greater than 3 months,[71,92,113] and at least 6 months.[14,74,86,87,91,104] In other papers, the majority of the participants were identified as having tinnitus for 3 years or more ,[88] 8.3 years,[112] 9.4 years,[7] and 13 years.[75] Other publications did not report on the duration of tinnitus prior to the intervention.[7,13,52,54,95]

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;[74,86,87,91] one study included only persons who had not received treatment elsewhere, or persons for whom previous treatments had failed.[52] In the inclusion criteria, tinnitus was identified as having to be a 'main' or 'major' complaint,[78] perceived as constant,[7] 'sufficiently bothersome to warrant intervention',[88] and as 'disabling chronic uni- or bi-lateral.'[99] Some studies required specific scores on tinnitus severity scales to meet study inclusion criteria. For example: a score of 10 or greater on the Tinnitus Reaction Questionnaire (TRQ);[91,92] a distress score greater than 17 points on the TRQ;[86,87] a score greater than 46 (high annoyance) on the Tinnitus Questionnaire (TQ) Modified version;[14] a score of greater than 40 on nine scales assessing the disruptive effects of tinnitus;[13] a Visual Analogue Scale (VAS) score (range=0-10) of greater than 3;[104] ≥30 on the Tinnitus Handicap Inventory (THI) scale;[112] and a tinnitus of grade 2 or 3.[7,138]

Interventions

CBT combined with biofeedback[14] and a psychophysiologic-oriented intervention combining CBT and relaxation components[104] were compared to waitlist controls. In one study[93] comparisons were made between four conditions: a waitlist control, the same CBT intervention administered by two different clinicians (TCT1 and TCT2). In another study,[87] comparisons were made between three conditions: a waitlist control and two types of cognitive intervention, ACI (attention control and imagery training) and CR (cognitive restructuring) provided alone or in combination. In another study,[86] comparisons were made between three conditions: a waitlist control, education alone, and CBT with education. An additional two studies compared CBT to other treatments: an information only intervention[71] or to internet-based self-help.[92] Three articles[54,88,112] evaluated forms of TRT. 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 waitlist control.[88] In the other study,[112] TRT was compared to a waitlist control and to ACT (acceptance and commitment therapy). A final additional study compared a combination of CBT and TRT to usual care.[54]

Three articles[7,13,52] compared interventions focused on relaxation to waitlist controls. In one of the studies,[52] 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 waitlist control could be made as well as comparisons between groups receiving the same or different instructions.

Some of the studies involving CBT, TRT and relaxation interventions listed above also included comparisons between other treatments and a waitlist control, including : education,[13] self-help book and brief phone therapy,[91] bibliotherapy,[95] Qigong therapy,[78] acceptance and commitment therapy (ACT),[112] and Yoga.[93] Others also included comparisons between two treatments, such as TRT and education[88] and TRT and ACT.[112] Three additional studies compared a waitlist control to other interventions, including bibliotherapy,[95] a self-help book and brief phone therapy,[91] and Qigong therapy.[78] A final study[113] compared three treatments to each other: tinnitus coping training (TCT), habituation-based treatment (HT) and education.

Comparators

Eight articles[13,14,74,75,86,87,93,104] compared no treatment[75] or a waitlist control[13,14,74,86,87,93,104] to various forms CBT administered either alone or in combination with other treatments.

Comparators for the articles assessing TRT included no treatment[88] and WLC.[112] For relaxation therapy the comparators were all WLC[7,13,52] and for other interventions they were also all WLC.[13,78,91,93,95,112]

Table 23. Psychological/Behavioral interventions and outcome measures

Psych/Beh Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
CBT / CBT combination		**INACTIVE COMPARISONS**							
	1	CBT vs. no treatment Andersson,[75] 2005		HADS-A*, ASI	HADS-D			TRQ	NR
	2	CBT via the internet vs. WLC Andersson,[74] 2002	VAS	HADS-A*, ASI	HADS-D	VAS		TRQ*, VAS-Ann, VAS-Ctrl	NR
	3	CR vs. WLC Henry JL and Wilson PH,[87] 1998			BDI			TRQ*, TEQ, THQ (handicap), TCSQ (coping)	NR
		CR combined with ACT vs. WLC Henry JL and Wilson PH,[87] 1998			BDI				NR
		ACT vs. WLC, Henry JL and Wilson PH,[87] 1998			BDI				NR
	4	CBT & Education vs. WLC Henry JL and Wilson PH,[86] 1996			BDI	Self-report		TRQ*, TEQ, THQ (handicap), TCSQ (coping), TCQ (Awareness)	NR
	5	CBT- biofeedback-based vs. WLC Weise,[14] 2008	VAS*, TQ-sub		BDI	VAS	GSI SCL-90R	TQ*, VAS TRSS (catastrophizing), TRCS (helplessness)	NR
	6	TCT1 vs. WLC Kroner-Herwig,[93] 1995	Diary, TQ subs*		Dep-Skala	Diary	Bef-Skala Bes-Liste*	Diary	NR
		TCT2 vs. WLC Kroner-Herwig,[93] 1995	Diary, TQ subs*		Dep-Skala	Diary	Bef-Skala Bes-Liste*	Diary	NR
	7	TCT vs. WLC Kroner-Herwig,[13] 2003			ADS	Diary	SCL-90R GSI	TDI TQ* TC (COPE subscales)	NR
	8	Psychophysiological therapy vs. WLC , Rief,[104] 2005				Diary	HRLS* GSI SCL-90R	TQ*, emotional cognitive distress	None

Table 23. Psychological/Behavioral interventions and outcome measures (cont'd)

Psych/Beh Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
		HEAD TO HEAD COMPARISONS							
	1	CBT vs. Information only Abbott,[71] 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,[92] 2008	ISI	HADS-A	HADS-D	VAS		THI TRQ, VAS	NR
	3	CBT vs. ACT Henry JL and Wilson PH,[87] 1998			BDI				NR
		CBT vs. CBT combined with ACT Henry JL and Wilson PH,[87] 1998			BDI				NR
		ACT vs. CBT combined with ACT Henry JL and Wilson PH,[87] 1998			BDI				NR
	4	CBT & Education vs. Education WLC Henry JL and Wilson PH,[86] 1996			BDI	Self-report		TRQ, TEQ, TCSQ coping, TCQ	NR
	5	TCT1 vs. TCT2 Kroner-Herwig,[93] 1995	Diary TQ		Dep-Skala	Diary	TQ Bef-Skala Bes-Liste*		NR
	6	TCT2 vs. Yoga Kroner-Herwig,[93] 1995	Diary TQ		Dep-Skala	Diary	TQ Bef-Skala Bes-Liste*		NR
		INACTIVE CONTROL							
TRT	1	Traditional Support Group (TRT principles) vs. no treatment Henry,[88] 2007						TSI	None
		Group education counseling (TRT principles) vs. no treatment Henry,[88] 2007						TSI	None
	2	TRT vs. WLC, Westin,[112] 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,[54] 2012			HADS		HUI	TQ THI (impairment)	None
	2	TRT vs. ACT, Westin,[112] 2011	ISI	HADS-A	HADS-D		QOLI	THI (Tinnitus Impact)	None

Table 23. Psychological/Behavioral interventions and outcome measures (cont'd)

Psych/Beh Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
		INACTIVE COMPARATOR							
Relaxation	1	Relaxation therapy vs. WLC Scott,[7] 1985			Self-report-R	Self-report-D		Self-report-D	yes
	2	Relaxation therapy Counter-demand vs. WLC Ireland,[52] 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
		Relaxation therapy Neutral-demand. vs. WLC Ireland,[52] 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
		Relaxation therapy Counter-demand -2vs. WLC Ireland,[52] 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
		Relaxation therapy Neutral-demand -2vs. WLC Ireland,[52] 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
	3	Relaxation vs. WLC Kroner-Herwig,[13] 2003			ADS	Diary	GSI SCL-90R	TDI (disability), TQ* TC (COPE-subscales)	NR
		HEAD to HEAD							
	1	Relaxation therapy Counter-demand vs. Neutral Demand Ireland,[52] 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
		Relaxation therapy-2 vs. Neutral-demand-2 Ireland,[52] 1985		STAI	BDI	Self-report		Tinnitus interference (self-report)	NR
Other		**INACTIVE COMPARATOR**							
	1	Education vs. WLC Kroner-Herwig,[13] 2003			ADS	Diary	GSI SCL-90R	TDI (disability), TQ* TC (COPE-subscales)	NR
	2	Self-help book and brief phone therapy vs. WLC Kaldo,[91] 2007	ISI	HADS-A	HADS-D	VAS		THI (handicap) TRQ*, VAS	NR
	3	Bibliotherapy vs. WLC Malouff,[95] 2010					GHQ-12	TRQ	None
	4	Qigong therapy vs. WLC Biesinger,[78] 2010						TBF-12*, VAS	None

Table 23. Psychological/Behavioral interventions and outcome measures (cont'd)

Psych/Beh Intervention		Specific Intervention	Sleep	Anxiety Symptoms	Depression Symptoms	Loudness	Global QOL	Tinnitus-Specific QOL	Adverse Events
	5	ACT vs. WLC, Westin,[112] 2011	ISI	HADS-A	HADS-D		QOLI	THI (Tinnitus Impact)	None
	6	Education alone vs. WLC Henry JL and Wilson PH,[86] 1996			BDI	Self-report		TRQ, TEQ THQ (handicap), TCSQ (coping), TCQ (Awareness)	NR
	7	Yoga vs. WLC Kroner-Herwig,[93] 1995	Diary TQ		Dep-Skala	Diary	TQ Bef-Skala Bes-Liste		NR
		HEAD TO HEAD							
	1	Traditional Support Group (TRT principles) vs. Group Education Henry,[88] 2007						TSI	None
	2	TRT vs. Acceptance Commitment Westin,[112] 2011	ISI	HADS-A	HADS-D		QOLI	THI (Tinnitus Impact)	None
	3	COMPLETE TRIAL -3 ARMS TCT = cognitive behavioral tinnitus coping training HT = habituation-based treatment EDU = educational control-group Zachriat,[113] 2004				Diary	VEV	TQ, TCQ, JQ , Diary(awareness)	NR
		TCT vs. EDU Zachriat,[113] 2004				Diary	VEV	TQ, TCQ, JQ, Diary(awareness)	NR
		TCT vs. HT Zachriat,[113] 2004				Diary	VEV	TQ TCQ JQ , Diary(awareness)	NR
		EDU vs. HT Zachriat,[113] 2004				Diary	VEV	TQ, TCQ, JQ, Diary(awareness)	NR

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

Abbreviations: 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 behaviour; vs. = versus; WLC = wait list control

Outcomes

Most studies reported data on more than one outcome (see 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 tinnitus-specific quality of life. 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.' A new outcome, 'tinnitus-specific quality of life,' was added, and combined the categories 'discomfort' and 'severity;' and all papers examined outcomes using validated measurement instruments within this domain.

Table 24. Outcome measurements used – Psychological/behavioral interventions

Outcome	Outcome Measurement Used
Sleep Disturbance	VAS (Visual Analog Scale)[14,71,74] ISI (Insomnia Severity Index)[91,92,112] TQ (Tinnitus Questionnaire subscale – sleep disturbance)[14,93] Diary[93]
Anxiety Symptoms	HADS-A (Hospital Anxiety and Depression Scale – Anxiety subscale)[74,75,91,92,112] DASS-A (Depression and Anxiety Stress Scale)[71] STAI (State-Trait Anxiety Inventory)[52] ASI (Arabic Scale of Insomnia)[74,75]
Depression Symptoms	HADS-D (Hospital Anxiety and Depression Scale – Depression subscale)[74,75,91,92,112] BDI (Beck Depression Inventory)[14,52,86,87] DASS-D (Depression and Anxiety Stress Scale)[71] ADS (A Depression Scale, The German version of CES-D "Center for Epidemiologic Studies Depression scale")[13] Self-report Retrospect[7] HADS (Hospital Anxiety and Depression Scale - Depression and Anxiety composite)[54] Depressivitats-Skala[93]
Subjective loudness	VAS (Visual Analogue Scale)[14,71,74,91,92] Self-rated/reported scale/score[7,52,86] Diary[13,93,104,113]
Global Quality of Life	HUI-3 (Health Utilities Index-3)[54] GSI (Global Severity Index – Symptom Checklist self-rating questionnaire)[14] WHO-Social (Quality of Life Questionnaire)[71] QOLI (Quality of Life Questionnaire Instrument)[112] SLR-90R (Symptom Checklist self-rating questionnaire)[13] HRLS (psychological symptoms short form of SCL-90R)[104] GSI (General Symptomatic Index)[104] GPD[95] VEV (Changes in wellbeing and adaptive behavior induced by treatment which go beyond modification of tinnitus related illness)[113] Befindlichkeits-Slala, Beschwerden liste[93] TQ[93]

Table 24. Outcome measurements used – Psychological/behavioral interventions (cont'd)

Outcome	Outcome Measurement Used
Tinnitus-Specific Quality of Life	TRQ (The Tinnitus Reaction Questionnaire)[71,74,75,86,87,91,92,95] TEO (Tinnitus Effects Questionnaire)[86,87] THQ (Tinnitus Handicapped Questionnaire)[86,87] TCSQ (Tinnitus Coping Strategies Questionnaire)[86,87] TCQ (Tinnitus Cognitions Questionnaire)[86,87,113] TQ (Tinnitus Questionnaire)[13,14,54,104,113] VAS (Visual Analogue Scale)[14,71,74,78,91,92] TRSS (Tinnitus-Related Self-Statements Scale)[14] TRCS (The Tinnitus-Related Control Scale)[14] TCT (Tinnitus Coping Training)[13] OSI-R (Occupational Stress Inventory–Revised)[71] THI (Tinnitus Handicap Inventory)[54,91,92,112] TSI (Tinnitus Severity Index)[88] Self-report Direct and Retrospect[7,52] TDI (Tinnitus Disability Questionnaire)[13] JQ (Jastreboff Questionnaire)[113] Diary (awareness)[113] TBF-12 (Tinnitus Questionnaire)[78] Diary-D,I,C,TQPQ, TQSC[93,113]

Setting

The research settings were in departments of audiology,[7,93,112] psychology,[113] psychology outpatient,[14] psychotherapy outpatient,[104] university clinic,[52] hospital (department not reported),[88] clinic,[52,54,92] phone/mail,[91] newspaper and radio advertisements,[87] and the internet.[71,74,75,92,95] Three papers did not report the research setting.[13,78,86]

Country

The studies were carried out in several different countries: Sweden;[7,74,75,91,92,112] the United States;[88] Australia;[52,71,86,87,95] Germany;[13,14,78,93,104,113] and the Netherlands.[54]

Sources of Funding

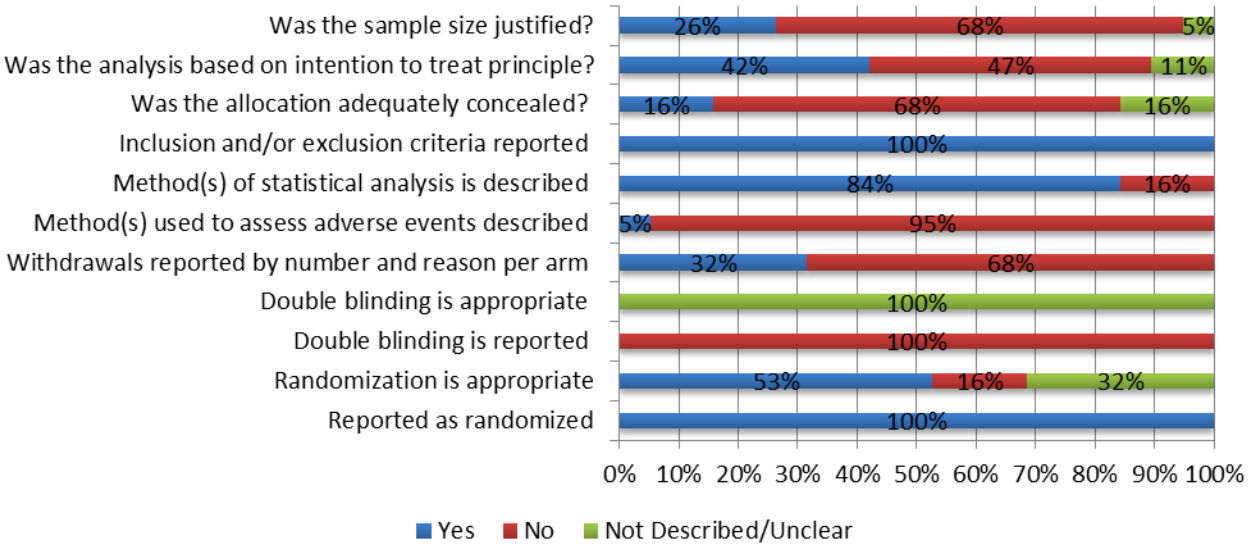
Sources of funding were not reported in seven studies.[52,78,86,87,92,93,104] Twelve publications received funding from research councils, foundations, and government departments and non-profit associations.[7,13,14,54,71,74,75,88,91,95,112,113]

Risk of Bias for Psychological/Behavioral Interventions

The risk of bias in the 19 RCTs evaluating psych/behavioral interventions was mixed (n=9 fair;[14,71,78,87,88,91,104,112,113] n=8 poor;[7,13,52,75,86,92,93,95] and n=2 good.[54,74] All authors reported their studies as randomized, with appropriate randomization in 53 percent (n= 10) of articles[14,54,71,74,78,88,91,104,112,113] and inappropriate randomization in three (16%).[13,92,95] The randomization method was not described in six articles (32%).[7,52,75,86,87,93] All articles did not involve double-blinding due to the nature of the interventions. All article reported the inclusion/exclusion criteria, and all but three (84%)[13,93,95] 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%),[7,13,14,52,75,86,88,92,93,95,104,112,113] no description of methods to assess adverse effects (n=18, 95%);[7,13,14,52,71,74,75,78,86-88,91-93,95,104,112,113] inadequate concealment of allocation (n=13, 68%);[7,13,52,75,78,86-88,91,92,95,104,112] analysis not based on intention-to-treat principle (n=9, 47%);[7,13,52,75,78,86-88,104] and inadequate justification of sample size (n=13, 68%).[7,13,52,71,75,78,86-88,91,93,95,113]

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 waitlist controls investigated the effects of 27 interventions on tinnitus-specific measures related to quality of life (QoL).[7,13,14,52,74,75,78,86-88,91,93,95,104,112] See Table 23.

The primary measures used to evaluate this outcome included: TRQ,[74,75,86,87,91,95] TQ,[13,14,104] THI,[112] TSI,[88] TBF-12,[78] TQ-PI,[93] and other single self-report items.[7,52] A variety of measures were also tested in addition to these primary measures.

Eight RCT studies evaluated the effect of eleven interventions in the CBT category on tinnitus-specific quality of life outcome measures. The TRQ questionnaire was used to measure tinnitus-specific outcomes in half of the studies in the CBT category which investigated six interventions.[74,75,86,87] A significant reduction in distress due to tinnitus was reported in a study in which CBT was delivered by internet[74] [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 two-hour group CBT sessions [$F(1,21)=6.4$, $p=0.02$].[75] A study of two types of cognitive intervention, CR and ACI delivered either alone or together[87] reported significant reductions in tinnitus distress for the CR, ACI and combined CR plus ACI interventions compared to the waitlist control [$F(1,46)=6.11$, $p<0.05$], but significantly more benefit was found when the intervention components were combined than when they were delivered alone. A study comparing a waitlist group to two treatments, a cognitive coping training combined with education and an education alone treatment,[86] 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 [$F(1,57)=16.19$, $p<0.01$]. The TQ was used as the outcome measure in four studies[13,14,93,104] of five interventions in the CBT category. A study[93] comparing a waitlist control 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 waitlist control group to a group receiving cognitive behavioral TCT intervention,[13] significant effects in favor of treatment were reported [$F(1,34)=9.22$, $p < 0.01$]. A psychophysiological CBT intervention[104] yielded a significant reduction in tinnitus distress on the TQ in comparison to the waitlist control group [group x time interaction: $F(1,41)=6.74$, $p < 0.05$, $g=0.64$], as did a biofeedback-based CBT intervention[14] [$F(1,109)=55.40$, $p < 0.001$, $g=1.15$].

Two RCT studies evaluated the effect of three interventions involving TRT on tinnitus-specific handicap using the THI or severity using the TSI. In one study,[112] compared to a waitlist control group, TRT did not yield a significant improvement on the THI immediately post-treatment. In the other study, a counseling intervention based on TRT was compared to traditional support or a waitlist control using the TSI;[88] although significant group effects were not found at the one-month followup, the study reported a significant pre- vs. post-treatment improvement on the TSI for the counseling intervention based on TRT and at the six-month and one-year followup the counseling intervention based on TRT yielded significantly greater improvements compared to either the waitlist or traditional support groups.

Three RCT studies evaluated the effect on tinnitus-specific quality of life for six interventions involving relaxation that were delivered to groups with sample sizes of less than 20.[7,13,52] A significant effect of treatment on the TDI was reported for a minimal contact relaxation intervention compared to the waitlist control group [$F(1,34)=6.79$, $p < 0.01$], but not on the TQ.[13] For the other interventions involving relaxation, tinnitus-specific outcomes were measured by a single self-report item. In one study,[7] 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 training in relaxation, self-control by distraction, and how to apply these methods in everyday situations.[7] In another study,[52] 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 two-week period.[52]

Seven RCT studies evaluated the effect of seven other psychological behavioral interventions on tinnitus-specific quality of life.[13,78,86,91,93,95,112] A significant reduction in tinnitus handicap as measured using the THI was reported in a study in which ACT was compared to a waitlist control group[112] [group x time interaction: $F(1,42)=12.16$, $p=0.001$]. One study[78] reported that Qigong (mindful exercise) was reported to significantly reduce 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,[93] 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 waitlist control group to a group receiving a minimal educational intervention,[13] no significant effect in favor of treatment were reported. As mentioned above, one study[86] evaluated the effect of CBT combined with education and an education alone intervention compared to a

waitlist control on TRQ score and did not find a significant effect of the education alone treatment. Two other studies evaluated the effects of treatment on tinnitus distress using the TRQ, one comparing a waitlist control to bibliotherapy[95] and the other to a self-help book with telephone therapy.[91] A significant reduction in tinnitus distress was found for the treatment involving a self-help book and telephone therapy[91] [group x time interaction: [$F(1,70)=12.4$, $p < 0.001$] and for the bibliotherapy intervention [$F(1,122)=6.23$, $p = .01$, $d=0.28$], but there was no significant effect when an intention-to-treat analysis was conducted for the bibliotherapy intervention.[95]

As seen in the forest plots (see 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 (less than a third of the interventions evaluated) 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 fairly wide variety of interventions, including biofeedback-based CBT, psycho-physiologic CBT, group CBT for elderly tinnitus sufferers, cognitive TCT, educational counseling, relaxation, self-help book with telephone therapy, and ACT.

Strength of Evidence - Tinnitus-specific Quality of Life

For the CBT studies, only one study had sample size greater than 50 subjects per group; as such the majority of studies had small sample sizes and lack of power calculations; we judged these studies to be relatively imprecise for this reason. We judged the direction of effect to be consistent across studies showing that the findings favored the CBT treatment and all but three studies were not statistically significantly different. The confidence intervals had significant overlap and the magnitude of the effect size were generally large (greater than -0.5) with the exception of two studies. 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 tinnitus related quality of life is rated as moderate (see Table 25); CBT interventions relative to inactive controls show improvement in tinnitus related QoL symptoms.

For relaxation therapy, the studies were at high risk of bias, and showed wide confidence intervals suggesting imprecision. 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 tinnitus related quality of life is rated as insufficient.

For TRT therapies, the two studies both favored treatment but only was significant. The confidence intervals overlapped to a large degree but the magnitude of the effect varied from small to large. One study had a very small sample size and given the lack of power calculations, these studies are considered imprecise. No dose response pattern was observed. Risk of publication bias is high given the small sample sizes of the studies. The SOE for TRT interventions for the outcome of tinnitus related quality of life is rated as insufficient.

When considering the interventions grouped in the “other category”, we deemed the evidence as insufficient given the high risk of bias and small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes of the study and the single studies within this group.

Table 25. Strength of evidence by psychological and behavioral interventions relative to inactive interventions for the treatment of tinnitus for the outcome of Tinnitus-specific Quality of Life for Psychological and Behavioral Interventions

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	8[13,14,74,75,86,87,93,104]	High	Consistent	Direct	Imprecise	-1.56 (-1.98,-1.13) to -0.13 (-0.93, 0.67)	Moderate
TRT vs. WLC or no treatment	N/A	2[88,112]	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[7,13,52]	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[13]	High	Unknown	Direct	Imprecise	-0.38 (-1.05, 0.28)	Insufficient
	Self-help and BPT vs. WLC	1[91]	High	Unknown	Direct	Imprecise	-0.64 (-1.16, -0.12)	Insufficient
	ACT vs. WLC	1[112]	High	Unknown	Direct	Imprecise	-1.12 (-1.76, -0.48)	Insufficient
	BLT vs. WLC	1[95]	High	Unknown	Direct	Imprecise	-0.33 (-0.68, 0.02)	Insufficient
	Qigong training vs. WLC	1[78]	High	Unknown	Direct	Imprecise	-0.14 (-0.82, 0.54)	Insufficient
	Yoga vs. WLC	1[93]	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/behav = psychological/behavioral; SMD = standard mean difference; SOE = strength of evidence; vs. = versus; TRT = Tinnitus Retraining Therapy; WLC = wait list control

Self-reported Loudness

Eight RCT studies with waitlist controls investigated the effects of 16 interventions on the subjective loudness of tinnitus.[7,13,14,52,86,91,93,104] 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 one week using a 10-point VAS to rate loudness,[14,91,104] a loudness rating item with a 4-point scale on a monitoring form that was completed daily for a one-week period[86] or a two-week period,[52] a daily diary entry (scale unspecified) completed over a two-week period,[13] 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'),[7] and a VAS 10-point scale with a loudness rating item that was completed three times per day over a two-week monitoring period.[93]

The effect on loudness was evaluated for six interventions in the CBT category. A significant beneficial effect of biofeedback-based CBT[14] was reported [group x time interaction: $F(1,109) = 10.83$, $p < 0.001$]. No significant effects of treatment on subjective loudness were reported for the other interventions in this category, including a CBT plus education intervention,[86] a CBT plus TCT intervention,[13] and a TCT intervention delivered by two different clinicians.[93]

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.[7,13,52] 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.[7] No significant effect of treatment on subjective loudness was reported for the other treatments in this category, including a minimal contact relaxation intervention,[13] and relaxation delivered with either neutral or counter-demand instructions to two different groups.[52]

The effect of loudness on four other psychological behavioral interventions was examined.[13,86,91,104] 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 were reported for education interventions[13,86] or for yoga.[93]

The forest plot (Figure 16) for subjective loudness as an outcome of treatment indicates that biofeedback-based CBT and intervention using a self-help book with telephone therapy show beneficial effects of treatment. Whereas 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

For the CBT studies, only one study had sample size greater than 50 subjects per group, as such the majority of studies had small sample sizes and lack of power calculations; we judged these studies to be relatively imprecise for this reason. We judged the direction of effect to be consistent across studies showing that the findings were almost always on the line of no effect; a single study favored CBT intervention and was statistically significant. With the exception of this single study, the magnitude of effect was small. Overall we judged these studies as consistent for subjective loudness. 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 loudness is rated as moderate (see Table 26); CBT interventions are not any different that inactive control with respect to this outcome.

For relaxation therapy, the studies were at high risk of bias, and 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 were showed statistically significant differences between groups. 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 loudness is rated as insufficient.

When considering the interventions grouped in the “other category”, we deemed the evidence as insufficient given the high risk of bias and small sample sizes. Risk of publication bias is high

for these interventions given the small sample sizes of the study and the single studies within this group.

Overall, it seems that there is little or no effect of treatment on subjective loudness, but the strength of evidence is low or insufficient (see Table 26).

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

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	6[13,14,74,86,93,104]	High	Consistent	Direct	Imprecise	-0.72 (-1.10,-0.33) to 0.01 (-0.61, 0.63)	Moderate
Relaxation vs. WLC	N/A	3[7,13,52]	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[13]	High	Unknown	Direct	Imprecise	0.21 (-0.45, 0.87)	Insufficient
	Self-help and BPT vs. WLC	1[91]	High	Unknown	Direct	Imprecise	-0.54 (-1.06, -0.03)	Insufficient
	Education vs. WLC	1[86]	High	Unknown	Direct	Imprecise	-0.27 (-0.89, 0.35)	Insufficient
	Yoga vs. WLC	1[93]	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

Five RCT studies with waitlist controls investigated the effects of interventions on sleep as a secondary outcome measure.[14,74,91,93,112] See Table 23.

In one study,[14] 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 waitlist control 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].

In a second study with 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 waitlist control: cognitive behavioral tinnitus coping training (TCT) administered by two clinicians (TCT-1 and TCT-2) and yoga. There was no significant effect of either treatment on sleep.

In two other studies with small sample sizes (30 or less per group), one investigating TRT and ACT[112] and the other[91] 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 therapy on sleep [time x group interaction $F(1,69) = 11.2$, $p < 0.001$], as well as a significant beneficial effect of ACT on sleep [time x group interaction $F(1,41) = 5.67$, p=0.022], but no significant effect of TRT.

The findings reported in the studies are in general agreement with moderate heterogeneity amongst outcomes shown in the forest plot. A significant beneficial effect on the VAS measure in favor of treatment for the biofeedback-based CBT[14] and a significant beneficial effect on the ISI of the self-help book with telephone therapy[91] can be seen in the forest plot, as well as a mean effect in favor of treatment for ACT.[112] No benefit from TRT,[112] TCT,[93] or yoga[93] 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

For the three CBT studies that evaluated sleep disturbance[14,74,93] two had very small sample sizes and the confidence intervals for the study with the smallest sample size had wide confidence intervals. We judge these studies to be imprecise as not all confidence intervals overlap. The direction of effect is generally consistent in that 3 of 4 studies favor treatment and only one of these is statistically significant; one study arm favors control but this is not statistically significant. The confidence intervals have some overlap and the magnitude of the effect size are moderate to large (-0.28 and -0.70) suggesting large variation in effect size; for this reason we judge the studies to be inconsistent.

With respect to risk of bias, the studies were categorized as high risk of bias and only one study 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 insufficient (see Table 27)

For TRT therapy interventions, the single study[112] shows a point estimate favoring control but this was not statistically significant. The study sample size is small and we judge this as imprecise. This single study is 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 size.. The SOE for TRT interventions for the outcome sleep disturbance is rated as insufficient.

When considering the interventions grouped in the “other category”, we deemed the evidence to inconsistent as not all intervals overlap and the magnitude of the effect sizes vary from small to large. The studies were at high risk of bias and the studies have small sample sizes. Given the heterogeneity of these interventions we rate each study as insufficient SOE.

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

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	3[14,74,93]	High	Inconsistent	Direct	Imprecise	-0.70 (-1.08, -0.31) to 0.61 (-0.23, 1.46)	Insufficient
TRT vs. WLC or no treatment	N/A	1[112]	High	Unknown	Direct	Imprecise	0.12 (-0.49, 0.72)	Insufficient
Other psych / behavioral	ACT vs. WLC	1[112]	High	Unknown	Direct	Imprecise	-0.55 (-1.16, 0.05)	Insufficient
	Self-help book + BPT vs. WLC	1[91]	High	Unknown	Direct	Imprecise	-0.60 (-1.07, -0.13)	Insufficient
	Yoga vs. WLC	1[93]	High	unknown	Direct	Imprecise	0.10 (-0.70, 0.89)	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

Anxiety

Five RCT studies[52,74,75,91,112] evaluated anxiety symptoms as one of the main outcomes[52,74,75] or as a secondary outcome[91,112] that was compared to a waitlist control group (see Table 23). The group mean pre-treatment scores on the STAI suggest that the participants had mild levels of anxiety[52] and results on the HADS-A[74,75,91,112] suggest that anxiety symptoms were minimal. Indeed, the HADS-A score was used in one study[91] as an eligibility criterion to rule out anxiety as a major problem. Two studies[74,75] 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.[75] However, in another study,[74] significant effects of CBT delivered by internet to a larger sample size were reported when the change scores for the treatment and waitlist 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].

When relaxation therapy was provided with either neutral or counter-demand instructions, there was no significant effect of treatment on anxiety was found using the STAI.[52]

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.[112] In another study,[91] a significant reduction in anxiety was reported when the treatment was a self-help book with telephone therapy [time x group interaction: $F(1,70) = 10.1$, $p = 0.002$].

As shown in the forest plot (see Figure 18), a clear beneficial effect on anxiety was found for the self-help book and telephone therapy,[91] 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,[112] but this study also has a high risk of bias. CBT delivered over the internet[74] and CBT delivered to a small group[75] have mean beneficial effects on anxiety, but these effects are not significant and the studies have moderate risk of bias. Relaxation[52] and TRT[112] seem to have little or no beneficial effect on anxiety.

Strength of Evidence – Anxiety Symptoms

There were two CBT intervention studies by the same author and one study was at low risk of bias and the other was at high risk of bias. Both studies show that treatment is favored relative to wait list control, but neither study was statistically significant. The magnitude of the effect size is moderate in both studies. The confidence intervals are wide for one study but the second study boundaries are overlapped completely. The sample sizes are small however, and the CI are large for one study; we consider the evidence to be imprecise. 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 (see Table 28)

For TRT therapy, Relaxation therapy, and "other" interventions, only single studies were evaluated and as such the consistency is unknown, the studies have wide confidence intervals and very small sample sizes and are therefore imprecise. Dose response cannot be assessed and risk of publication bias is high for these interventions given the small sample sizes.

Table 28. Strength of evidence by psychological and behavioral interventions relative to inactive interventions for the treatment of tinnitus for the outcome of Anxiety Symptoms for Psychological and Behavioral Interventions

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	2[74,75]	Moderate	Consistent	Direct	Imprecise	-0.38 (-1.21, -0.44) to -0.27 (-0.76, 0.22)	LOW
TRT vs. WLC or no treatment	N/A	1[112]	High	Unknown	Direct	Imprecise	-0.19 (-0.80, 0.41)	Insufficient
Relaxation vs. WLC	N/A	1[52]	High	Inconsistent	Direct	Imprecise	-0.08 (-1.26, 1.11) to 0.46 (-0.65, 1.57)	Insufficient
Other psychological	ACT vs. WL	1[13]	High	Unknown	Direct	Imprecise	-0.58 (-1.18, 0.03)	Insufficient
	Self-help book and BPT vs. WLC	1[91]	High	Unknown	Direct	Imprecise	-0.61 (-1.13, -0.09)	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

Depression Symptoms

Eleven RCT studies[7,13,14,52,74,75,86,87,91,93,112] investigated the effects of treatments on depressive symptoms by comparing treatments to waitlist controls (see Table 23). The BDI was used to measure depressive symptoms in four studies,[14,52,86,87] the HADS-D was used in four studies,[74,75,91,112] the ADS was used in one study,[13] a retrospective measure was used in one study[7] and the Depressivitäts Skala was used in one study.[93] As well, the ATQ was used as a second measure of depressive symptoms in one study.[87] Note that depression was used as a primary outcome measure in some studies,[52,74] but in most studies[7,13,14,75,86,87,91,93,112] it was considered to be only a secondary or general outcome measure that was not specifically related

to tinnitus. Also note that the eligibility criteria for some studies selected for participants who did not have major problems with depression[91] and the mean pre-treatment scores on standardized measures of depression indicated no more than mild depression.

Seven studies tested treatments in the CBT sub-category,[13,14,74,75,86,87,93] three using the BDI,[14,86,87] two using the HADS-D,[74,75] one using the ADS[13] and one using the Depressivitäts Skala to evaluate the same treatment administered by two different clinicians.[93] Some beneficial effects of treatment were reported in four studies[14,74,87,93] and no significant effects were reported in the other three.[13,75,86]

The effects on depression as measured with the BDI were studied in three studies in the CBT sub-category[14,86,87]: one CBT intervention consisted of 8 weekly sessions involving attention control and imagery and cognitive restructuring (ACI + CR) compared to an ACI-only treatment, a CR-only treatment and a waitlist control,[87]another CBT intervention was a 12-session biofeedback-based CBT delivered over 3 months compared to a waitlist control,[14] and a third CBT intervention was an 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 waitlist control.[86] In the study comparing ACI and CR treatments alone and in combination, it was reported that those who received treatment improved more than the waitlist control group [$F(1,46)=7.28$, $p <0.01$);[87] 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 waitlist control did not reach significance in the intention-to-treat analysis.[14] There was no significant effect on depression of the cognitive coping skills or education treatments on depressive symptoms.[86]

The CBT interventions evaluated using the HADS-D included one intervention with 6 weekly group sessions for adults 65 years of age and older that was compared to a waitlist control group who later received a shorter version of the treatment,[75] and an internet-based intervention with six self-help modules that was compared to a waitlist control.[74] For the treatment provided to older adults,[75] there was no effect on depression measured, whereas for the internet intervention,[74] 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 [$F(1,94)=5.4$, $p=0.02$].

The ADS, a German version of the CES-D to evaluate the effect on depressive symptoms of an 11-session CBT Tinnitus Coping Training (TCT) group intervention was compared to a waitlist control as well as two minimal-contact (MC) interventions, one entailing two group sessions focused on education about tinnitus (MC-E) and the other four group sessions focused on education and also music-supported relaxation (MC-R).[13] 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 waitlist control and also to yoga.[93] 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.

Three interventions focused on relaxation were evaluated: one treatment was the music-supported relaxation (MC-R) intervention that was compared to CBT in the study mentioned above,[13] one involved relaxation with neutral or counter-demand instructions with each version

of the treatment delivered to two groups or stages,[52] and the third was a treatment emphasizing coping through the use relaxation and distraction techniques.[7] As already noted above, there was no significant effect of the MC-R as measured with the ADS.[13] 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 waitlist control groups. For the study using relaxation and distraction to enable coping,[7] depressive symptoms were measured using a visual analogue scale whereby participants marked a 10cm line (from 'none' to 'maximal') at the end of the day for periods of four 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 ($F(1,21)=4.76$, $p<0.05$).

The effect of TRT on depressive symptoms was evaluated in one study,[112] but no significant effects were found.

Five studies[13,86,91,93,112] investigated the effects of other treatments on depressive symptoms. The same study that evaluated the effect of TRT on depressive symptoms using the HADS-D also evaluated the effect of ACT and again found no significant benefit of treatment [20055]. The study already mentioned that investigated the effects of TCT using the ADS also evaluated the effects of education (ME-E) on depressive symptoms, with no significant benefit reported.[13] The study already mentioned that used the BDI to investigate the effects on depressive symptoms of CBT with education also evaluated the effects of education alone and found no significant benefit.[86] As mentioned above, no significant effect of yoga on depressive symptoms was reported.[93] Finally, an additional study[91] used the HADS-D to investigate the effect on depressive symptoms of a treatment involving a self-help book and telephone therapy and a significant beneficial effect was found [time x group interaction; $F(1,70)=5.3$, $p=0.024$].

The forest plots (see Figure 19) are consistent with the findings reported in the studies regarding the effect of the treatments on depressive symptoms. Overall, less than half of the treatments yielded a significant effect in favor of the treatment in comparison to a waitlist control.

Strength of Evidence – Depression Symptoms

Seven studies evaluated CBT interventions and the outcome of depressive symptoms, only one study had sample size greater than 50 subjects per group; as such the majority of studies had small sample sizes and lack of power calculations; we judged these studies to be relatively imprecise for this reason. We judged the direction of effect to be consistent across studies showing that the findings favored the CBT treatment in all but one study; only one study showed statistical differences and the remaining studies did not. The confidence intervals had significant overlap and the magnitude of the effect size varied from small were generally large (greater than -0.5) with the exception of two studies. 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 (see Table 29)

For TRT therapy interventions, a single studies at high risk of bias evaluated this outcome and as such the consistency is unknown, the study has a small sample sizes and are therefore

considered imprecise. Dose response cannot be assessed and risk of publication bias is high for these interventions given the small sample sizes.

For Relaxation therapies 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 we judge these studies to be inconsistent. The confidence intervals were widely varying and the sample sizes were very small in these studies and we rate them as 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.

When considering the interventions grouped in the "other category", we deemed the evidence as insufficient given the high risk of bias for all studies, unknown consistency, and small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes of the study and the single studies within this group.

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

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[13,14,74,75,86,87,93]	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[112]	High	Unknown	Direct	Imprecise	0.05 (-0.55, 0.66)	Insufficient
Relaxation vs. WLC	N/A	3[7,13,52]	High	Inconsistent	Direct	Imprecise	-1.85 (-3.59, -0.11) to -0.06 (-1.24, 1.13)	insufficient
Other psychological	ACT vs. WLC	1[112]	High	Unknown	Direct	Imprecise	-0.19 (-0.78, 0.40)	Insufficient
	Self-help and BPT vs. WLC	1[91]	High	Unknown	Direct	Imprecise	-0.54 (-1.06, -0.02)	Insufficient
	MC-E vs. WLC	1[13]	High	Unknown	Direct	Imprecise	-0.31 (-0.97, 0.35)	Insufficient
	Education vs. WLC	1[86]	High	Unknown	Direct	Imprecise	0.08 (-0.54, 0.70)	Insufficient
	Yoga vs. WLC	1[93]	High	Unknown	Direct	Imprecise	-0.32 (-1.12, 0.48)	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

Global Quality of Life

Six RCT studies[13,14,93,95,104,112] investigated the effects of treatments on non-tinnitus-specific global quality of life by comparing treatments to waitlist controls (see Table 23). 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'[13,14] and it was listed as a secondary outcome measure in one of those studies;[14] the GHQ-12 was used in one study[95] to measure general psychological distress; the German Beschwerden-Liste was used to measure various symptoms of well-being in one study;[93] the QoLI was used in one study[112] as a secondary outcome measure of quality of life based on responses in six domains; the HRLS was used in one study[104]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 quality of life was evaluated for five interventions in the CBT category. A significant effect favoring CBT was found for an intervention using biofeedback-based CBT[14] which was evaluated with the SCL-90-R [group x time interaction: $F(109)=7.61$, $p<0.01$]. No significant effect of treatment was reported for CBT using a psychophysiologic approach evaluated with the HRLS.[104] CBT with TCT and TCT were evaluated in two studies, one using the SCL-90-R[13] and the other using the Beschwerden-Liste;[93] no significant immediate post-treatment effects between the waitlist control and the treatment groups were reported in either study.

The effect on global quality of life by TRT was evaluated in one study[112] using the QoLI, but no significant effect of treatment was reported.

The effect on global quality of life by a relaxation intervention with minimal contact was evaluated in one study[13] using the SCL-90-R, but no significant effect of treatment was reported.

The effect on global quality of life was evaluated for four other psychological behavioral treatments: ACT[112] with the QoLI, bibliotherapy with the GHQ-12,[95] education with minimal contact with the SCL-90-R,[13] and yoga with the Beshwerden-Liste.[93] No significant effects of treatment on global quality of life were reported for ACT,[112] education,[13] or yoga.[93] However, a significant reduction in general stress measured with the GHQ-12 with a small effect size was reported for bibliotherapy.[95]

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.

Strength of Evidence – Global QoL

Four studies evaluated global quality QoL and CBT interventions. All studies were at high risk of bias. Only one study had a size greater than 50 subjects per group and the confidence intervals were widely varying; as such the majority of studies had small sample sizes and lack of power calculations; we judged these studies to be relatively imprecise for this reason. The direction of effect across studies showed that the findings favored the control group except for one study; however, all but one study (marginally significant) showed no statistically significantly differences. The confidence intervals had significant overlap and the magnitude of the effect size varied from small to large and we rated these studies 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 CBT interventions for the outcome of depression symptoms is rated as insufficient. (see Table 30)

For TRT interventions, Relaxation therapy, and "other category" interventions, we deemed the evidence as insufficient given the high risk of bias, unknown inconsistency, and wide confidence intervals small sample sizes. Risk of publication bias is high for these interventions given the small sample sizes of the study and the single studies within this group.

The small sample sizes and heterogeneity in the interventions and measurement tools provides insufficient strength of evidence to make conclusions regarding the effectiveness of the treatments in terms of global quality of life. See Table 30.

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

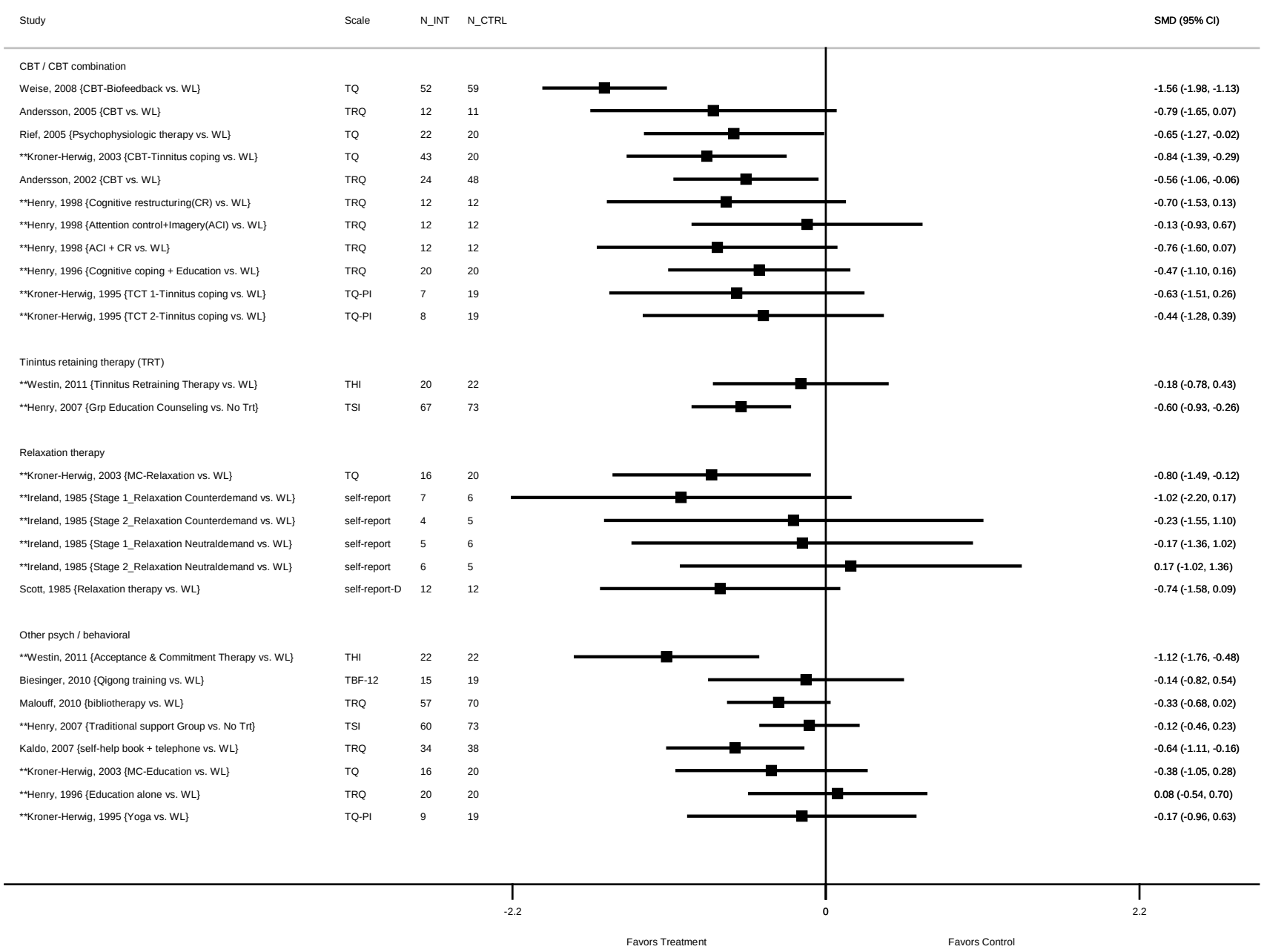
Intervention Group	Specifics	# of Studies (n)	Risk of Bias	Consistency	Directness	Precision	Magnitude of the effect SMD range (CI)	SOE
CBT/ CBT combination vs. WLC or no treatment	N/A	4[13,14,93,104]	High	Inconsistent	Direct	Imprecise	0.64 (0.02, 1.26) to -0.06 (-0.59, 0.47)	Insufficient
TRT vs. WLC or no treatment	N/A	1[112]	High	Unknown	Direct	Imprecise	0.06 (-0.55, 0.66)	Insufficient
Other psychological	ACT vs. WL	1[112]	High	Unknown	Direct	Imprecise	0.15 (-0.44, 0.75)	Insufficient
	BLT vs. WLC	1[95]	High	Unknown	Direct	Imprecise	0.45 (0.1, 0.81)	Insufficient
	MC-E vs. WLC	1[13]	High	Unknown	Direct	Imprecise	0.32 (-0.35, 0.98)	Insufficient
	Yoga vs. WLC	1[93]	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

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

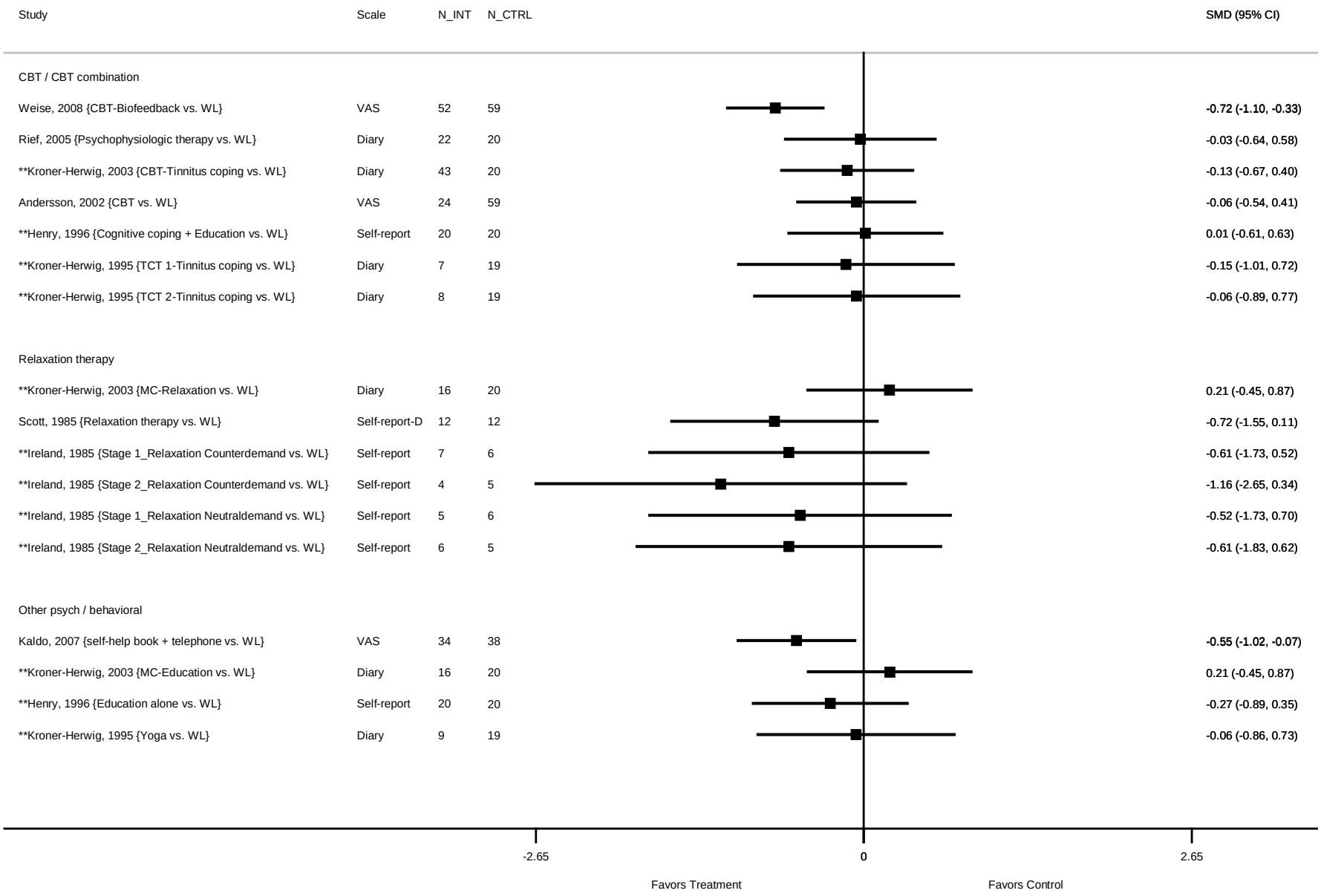
No data addressing this question were identified in the literature search.

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



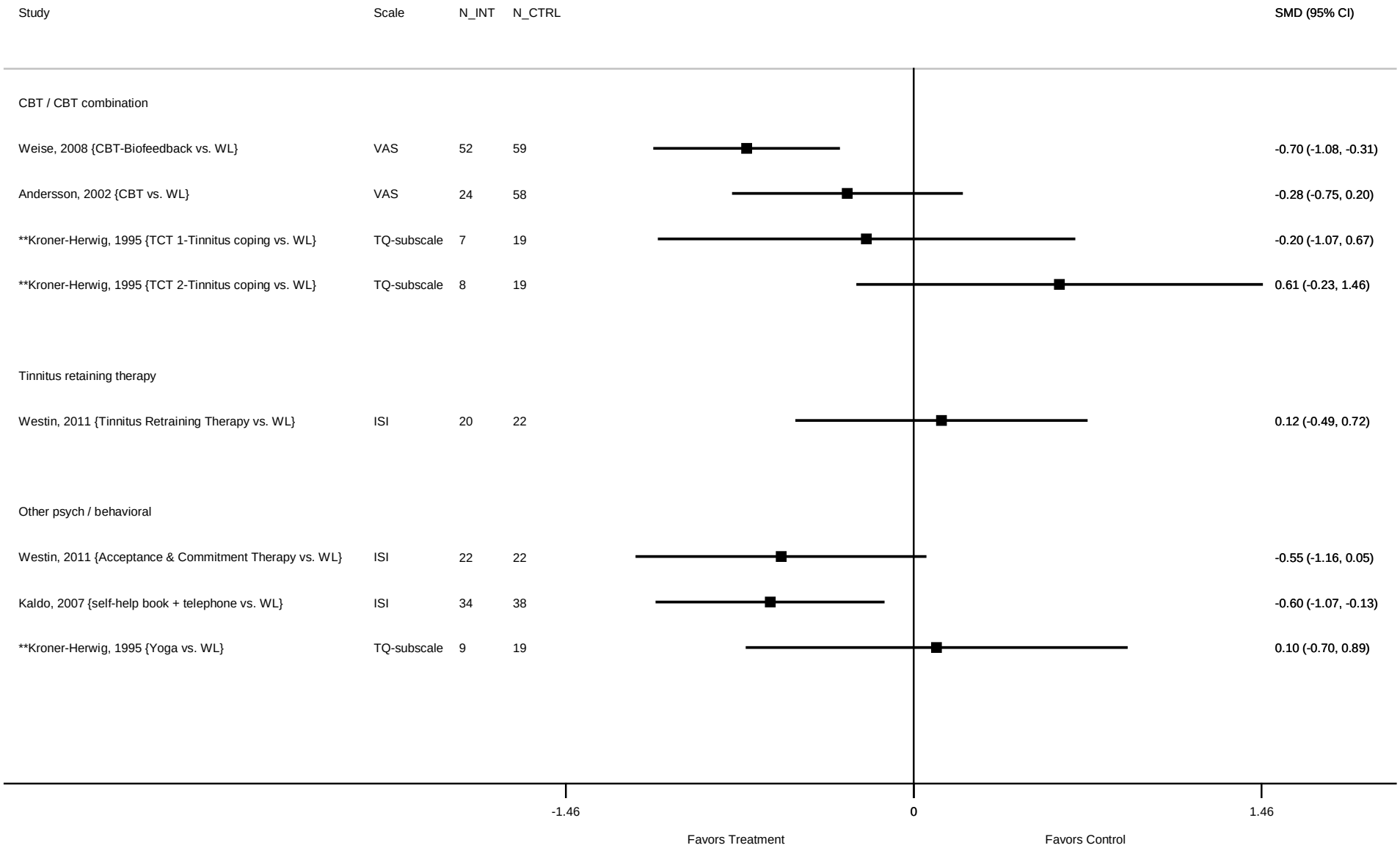
** Represent studies with multiple intervention groups

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



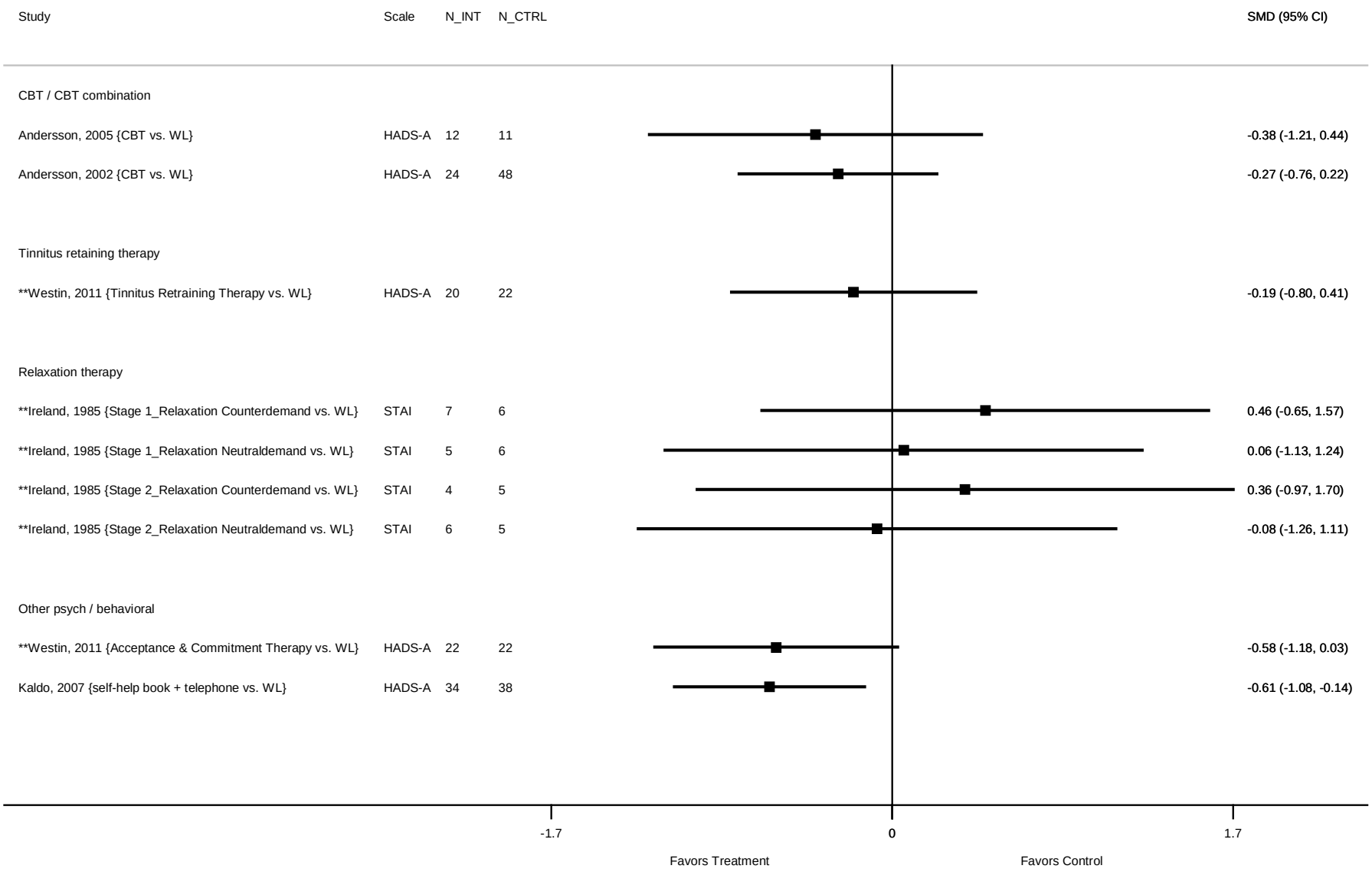
** Represent studies with multiple intervention groups

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



** Represent studies with multiple intervention groups

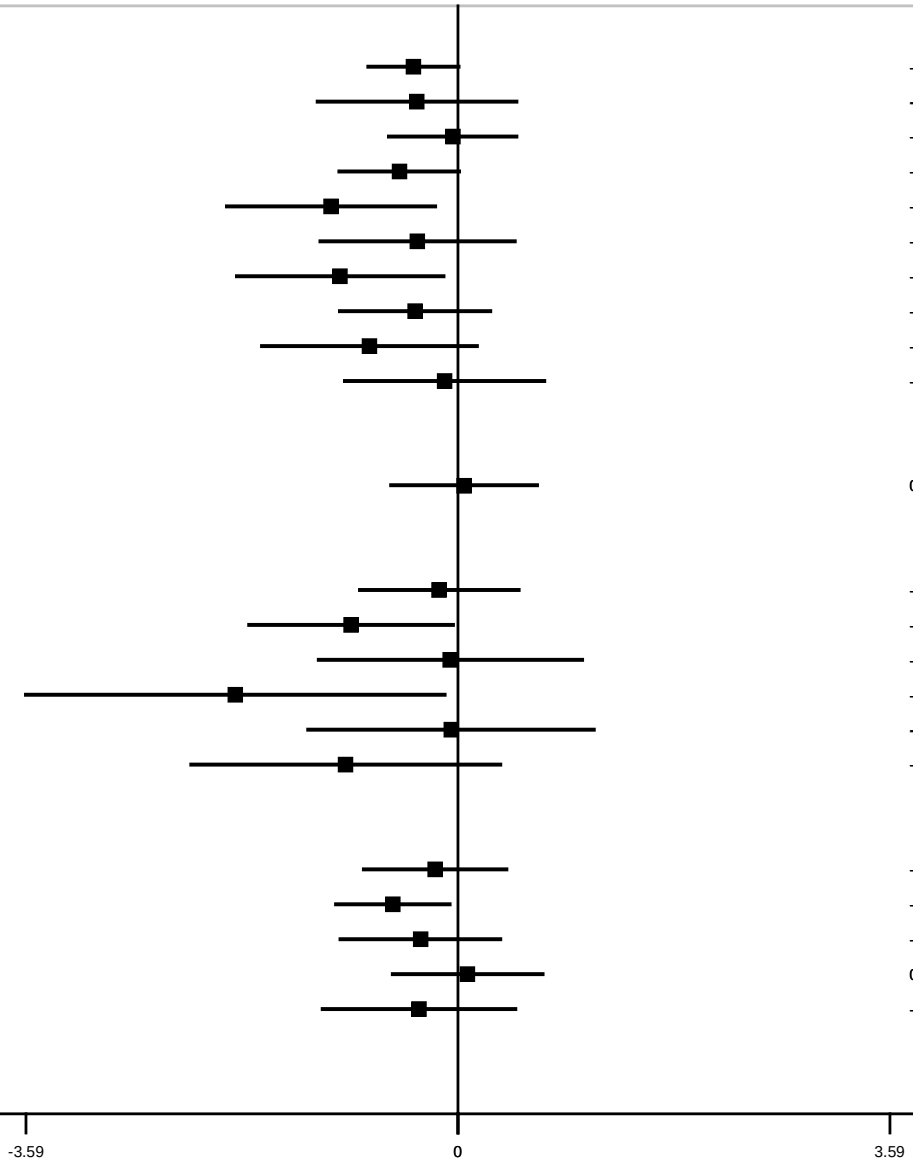
Figure 18. Studies with inactive comparators that evaluate psychological and behavioral interventions and report anxiety symptoms outcomes



** Represent studies with intervention groups

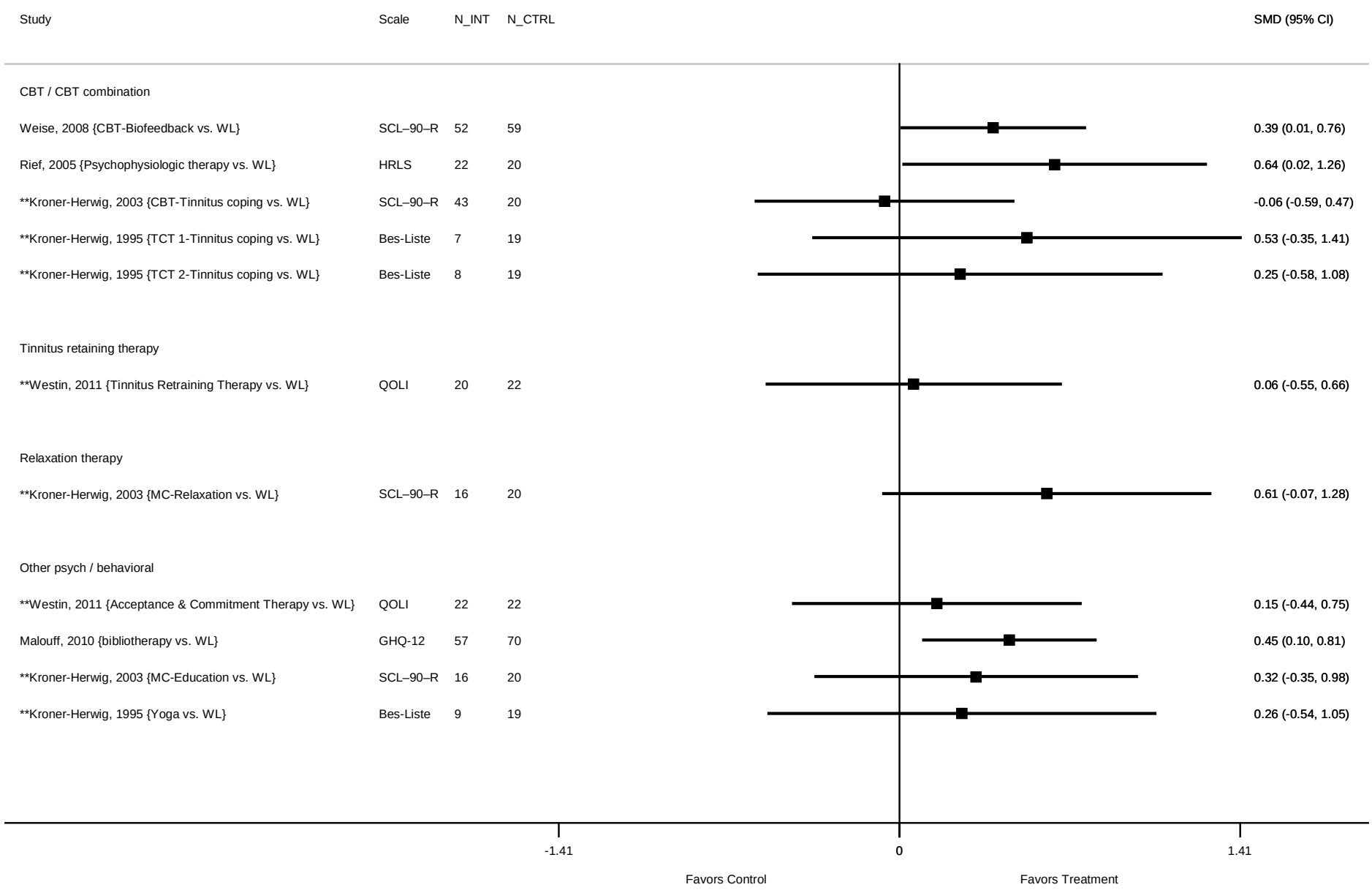
Figure 19. Studies with inactive comparators that evaluate psychological and behavioral interventions and report depressive symptoms outcomes

Study	Scale	N_INT	N_CTRL	SMD (95% CI)
CBT / CBT combination				
*Weise, 2008 {CBT-Biofeedback vs. WL}	BDI	52	59	-0.37 (-0.74, 0.01)
Andersson, 2005 {CBT vs. WL}	HADS-D	12	11	-0.34 (-1.16, 0.49)
**Kroner-Herwig, 2003 {CBT-Tinnitus coping vs. WL}	ADS	43	20	-0.04 (-0.57, 0.49)
Andersson, 2002 {CBT vs. WL}	HADS-D	24	48	-0.49 (-0.98, 0.01)
**Henry, 1998 {Cognitive restructuring(CR) vs. WL}	BDI	12	12	-1.05 (-1.92, -0.19)
**Henry, 1998 {Attention control+Imagery(ACI) vs. WL}	BDI	12	12	-0.34 (-1.14, 0.47)
**Henry, 1998 {ACI + CR vs. WL}	BDI	12	12	-0.98 (-1.83, -0.12)
**Henry, 1996 {Cognitive coping + Education vs. WL}	BDI	20	20	-0.35 (-0.98, 0.27)
**Kroner-Herwig, 1995 {TCT 1-Tinnitus coping vs. WL}	Dep-Skala	7	19	-0.73 (-1.63, 0.16)
**Kroner-Herwig, 1995 {TCT 2-Tinnitus coping vs. WL}	Dep-Skala	8	19	-0.11 (-0.94, 0.72)
Tinnitus retaining therapy				
**Westin, 2011 {Tinnitus Retraining Therapy vs. WL}	HADS-D	20	22	0.05 (-0.55, 0.66)
Relaxation therapy				
**Kroner-Herwig, 2003 {MC-Relaxation vs. WL}	ADS	16	20	-0.15 (-0.81, 0.50)
Scott, 1985 {Relaxation therapy vs. WL}	self-report-R	12	12	-0.89 (-1.73, -0.04)
**Ireland, 1985 {Stage 1_Relaxation Counterdemand vs. WL}	BDI	7	6	-0.06 (-1.15, 1.03)
**Ireland, 1985 {Stage 2_Relaxation Counterdemand vs. WL}	BDI	4	5	-1.85 (-3.59, -0.11)
**Ireland, 1985 {Stage 1_Relaxation Neutraldemand vs. WL}	BDI	5	6	-0.06 (-1.24, 1.13)
**Ireland, 1985 {Stage 2_Relaxation Neutraldemand vs. WL}	BDI	6	5	-0.93 (-2.21, 0.35)
Other psych / behavioral				
**Westin, 2011 {Acceptance & Commitment Therapy vs. WL}	HADS-D	22	22	-0.19 (-0.78, 0.40)
Kaldo, 2007 {self-help book + telephone vs. WL}	HADS-D	34	38	-0.54 (-1.01, -0.07)
**Kroner-Herwig, 2003 {MC-Education vs. WL}	ADS	16	20	-0.31 (-0.97, 0.35)
**Henry, 1996 {Education alone vs. WL}	BDI	20	20	0.08 (-0.54, 0.70)
**Kroner-Herwig, 1995 {Yoga vs. WL}	Dep-Skala	9	19	-0.32 (-1.12, 0.48)



** Represent studies with multiple intervention groups

Figure 20. Studies with inactive comparators that evaluate psychological and behavioral interventions and report global



** Represent studies with multiple intervention groups

Discussion

Overview

In a rehabilitative context, discomfort from tinnitus is more often the reason for seeking medical attention than hearing loss. 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.[55] Tinnitus is a complex condition for which a variety of interventions (some tinnitus-specific and others generic) have been applied. This Comparative Effectiveness Review (CER) attempted to evaluate key questions (KQ) (KQ1 and KQ3) 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 these questions (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 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 all of the KQ is presented below.

Key Question 1. In patients with symptoms of tinnitus (e.g., ringing in the ears, whoosing sounds) what is the comparative effectiveness of methods used to identify patients for further evaluation or treatment?

The criteria for including studies allowed methods that involved direct observation or observation of sound with a stethoscope, referral to a health professional with expertise on managing tinnitus (i.e., otolaryngologist, audiologist, neurologist, mental health professional), and the administration of scales/questionnaires to assess severity (e.g., Tinnitus Handicap Inventory [THI], Tinnitus Reaction Questionnaire [TRQ], Tinnitus Functional Index [TFI], Visual Analog Scale [VAS], and Tinnitus Severity Index [TSI]). However, these studies were restricted to primary and specialty care (e.g., audiology, otolaryngology, neurology, mental health care) with the specific outcomes of the method establishing any of the following: 1) no treatment necessary; 2) need for specialized treatment (e.g., audiology, otolaryngology, neurology, mental health care); and, 3) extent of intervention. This last criteria was the one that most affected eligibility for this systematic review.

Although there are several validated questionnaires[19] currently being used for assessing the symptoms and the impact of tinnitus, none were contrasted 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 nonsignificant 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 and less about 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 (such as patient reported questionnaires) encompassing multiple areas of quality of life or symptoms. Specifically, many of the tinnitus-specific measures (see Table 5) include questions concerning multiple outcomes of interest in the present review. However, 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 stroke[139]). 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.

Key Question 2. 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 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 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.[14] Rather, the reaction to the sound suggests that it is more than just an auditory problem; tinnitus often entails psychological distress.[8] Nevertheless, new sound generating technologies continue to be developed and tested.[108] 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 focused on adverse effects related to tinnitus symptoms (worsening of tinnitus, sedation symptoms, and surgical complications). From these, the strength of evidence (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 (e.g.,[83]). 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 (see Appendix G) 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 (i.e., CBT, mindfulness, specialized behavioral programs, neuro-music therapy versus behavioral music therapy, and educational interventions [see Appendix G]). Overall, this reflects significant research activity in interventions aimed at remediating problems associated with idiopathic tinnitus using a wide range of interventions.

Studies Involving Pharmacological and Food Supplement Interventions:

Overview of Findings

A total of 16 unique studies[24,72,76,77,81,84,97,98,101,103,105-107,109,111,114] evaluated the efficacy of pharmacological interventions or food supplements in tinnitus. The studies examined 6 outcomes: tinnitus-specific quality of life (QoL), subjective loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global QoL. A 17th article[90] contained additional data to supplement one of the study publications.[114]

The included articles evaluated 14 different interventions, all of which were compared to some form of placebo. In one study,[98] all participants received clonazepam and the treatment under evaluation was Deanxit, with the comparator being placebo. 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: nortriptyline[107] and honeybee larvae[76] for depression; alprazolam[24] and zinc[77] for loudness; and

acamprosate[72] for tinnitus-specific QoL measured as 'disturbance'. One study[107] found conflicting results for tinnitus-specific QoL (e.g., improved QoL or no difference compared to placebo) 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 depressive symptoms, although the reduction failed to reach statistical significance at the 5% level on one of the three scales used to measure depression.

Interpreting the Results – Issues to Consider

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.[114] 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 these treatments are not 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[84,101,105] did not find differences between the treatment and placebo groups, we cannot use these results 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 (i.e., gingko biloba[84,103]). 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 study[114] 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 follow-up 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 follow-up (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 (VAS and validated instruments alike). We recommend 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 they claim are clinically important.

Another important issue to consider is an instrument's ability to discriminate between treatment effects across study groups (in other words, the instrument's 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 instrument's discriminative ability 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.

Medical Interventions

Eleven studies evaluated four different types of medical interventions that included rTMS,[73,79,94,96,102] electromagnetic stimulation,[85] low level laser therapy (LLLT),[31,80,99] acoustic coordinated reset neuromodulation (ACRN),[108] and acupuncture.[110] Almost all studies in this grouping evaluated tinnitus-specific QoL. In general, the strength of evidence (SOE) for tinnitus related QoL 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 tinnitus related QoL, 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 tinnitus-specific QoL scores) occurred with low frequency rTMS (1 Hz) up to 6 months followup[73] but this single study was at high risk of bias. Our review also showed that adverse events were generally poorly evaluated and reported. A previous systematic review[140] 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. With respect to the interventions of ACRN, LLLT, and acupuncture, SOE was rated as insufficient for tinnitus-specific QoL.

When considering the outcome of perceived loudness, there were only five trials that evaluated this outcome[31,79,99,108,110] 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;[99] we judged this trial to have insufficient SOE. No studies evaluated the effect on sleep disturbance and global quality of life with these interventions.

All 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 distract a person's attention away from tinnitus has led to the use of maskers for tinnitus. This strategy 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[46,83,89,100] and a related study[82] 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,[89] 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,[100] whether benefit from an information intervention was augmented by the addition of a white-noise generator and/or relaxation,[83] and whether or not benefit depended on the type of stimulation used in Neuromonics Tinnitus Training.[46] While benefits from treatment were reported in some studies (specifically, benefit from treatment was reported for tinnitus-specific QoL based on THI scores), subjective tinnitus loudness and global QoL for the TRT interventions with either sound generators or open ear hearing aids[100] and benefit from tinnitus-specific QoL based on TRQ scores was reported for the Neuromonics Tinnitus Training with either type of stimulation.[46] 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,[83,89] pre-/post-treatment comparisons were analyzed to establish that there were actually any benefits from intervention, although the significance of differences in the effects of the treatments was tested statistically. In all cases the varieties of treatment evaluated were primarily focused on determining if 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 loss[100]). The comparison of

treatments' measurement issues are similar and perhaps even more challenging when compared to the issues raised above 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 evaluating a different set of eligible studies derived a similar conclusion suggesting insufficient evidence[141] or remarked upon the diversity of interventions and the lack of evidence overall.[142]

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 moderate strength for CBT and coping approaches, suggesting moderate confidence that the studies evaluating these interventions reflect the true effect for the two outcomes of importance analyzed (i.e., tinnitus-specific QoL and sleep). Note that the apparent absence of benefits from treatment for outcomes related to anxiety and depressive 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 tinnitus-specific QoL and CBT related interventions and rated the evidence as moderate[141] or showed evidence of benefit.[48,141-143] One of these previous reviews suggest that the evidence shows that CBT interventions do not affect depression and anxiety symptoms,[142] and other reviews suggests the evidence demonstrates that CBT improves depression scores[48] or mood.[143] One review showed no evidence of CBT affecting subjective loudness.[48]

Behavioral interventions (i.e., relaxation, education, TRT) employed an isolated approach that did not confer the same degree of benefit and were rated as low SOE, being plagued with the same problems as the studies evaluating pharmacological and medical interventions. It was observed that CBT combined with other behavioral interventions (EMG biofeedback in this review) were common treatment options. It is interesting that there is active the development of progressive[42,53] or staged treatments,[54] which could be a promising avenue to further explore 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 multi-modal interventions.

Key Question 3. 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 KQ that met inclusion criteria. Although most studies identified baseline population characteristics (i.e., age, duration and severity of tinnitus, comorbidities, etc.), 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

The study populations in the eligible literature were relatively homogenous yet were limited to predominately middle aged (≥50 years of age) persons suffering predominantly from subjective idiopathic tinnitus of mild to moderate severity. We cannot draw conclusions about the efficacy of the therapies in persons younger than 42 years of age, despite the fact that a recent survey estimated tinnitus was prevalent in 12.2 percent of the US population under 44 years of age.[105,144] It also 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.[145] This suggests that reports of tinnitus tended to increase with more recent birth cohorts compared with earlier birth cohorts; participants in a given generation were significantly more likely to report tinnitus than participants from a generation 20 years earlier (odds ratio [OR]=1.78, 95% CI, 1.44 to 2.21).

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[46,83,100] and even to 18 months for one study.[89] 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 weeks[7] to 2 months,[52] or 3 months[75,78,93] to 6 months,[87] but most continued to 1 year[13,74,86,88,91,95] or even 18 months.[112] 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 which are usually provided by rehabilitative professionals such as audiologists and psychologists whose practice may put greater emphasis on establishing as well as 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,[88] 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.[75]

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.

Most 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.[74] 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, data across interventions based on the end of treatment and longest followup time was presented. This makes comparison across studies and interventions challenging.

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, we assumed that our gropuings of studies were at risk.[69]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: tinnitus-specific QoL, subjective loudness, sleep disturbance, anxiety symptoms, depression symptoms, and global QoL. Little evidence was found to suggest that the therapies led to improvements over placebo on any of these outcomes. Our results are in agreement with the conclusions of previous systematic reviews, which found insufficient, inconsistent, or no evidence of treatment effects.[141,142,146-149]

In terms of strength of evidence (SOE), we have low confidence in 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 strength of evidence for rTMS and insufficient evidence for LLLT, ACRN, and acupuncture for improving tinnitus-specific quality of life. However, the studies were generally at high risk of bias, with small sample sizes and were poorly reported. Similarly, few studies evaluated subjective loudness, anxiety symptoms, and depression symptoms and as such 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, 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=8) and related treatments, TRT-related treatments (n=2), treatments involving primarily relaxation (n=3), and other interventions (n=7), including two involving reading tinnitus books, two emphasizing education, one with yoga, one with Qigong, and one with ACT. Outcomes for tinnitus-specific QoL (19 treatments), subjective loudness (13 treatments), sleep (6 treatments), anxiety (9 treatments), depressive 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 outcomes of anxiety and depression 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 moderate SOE for the outcomes of tinnitus related QoL and perceived loudness, 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 events were largely not reported in this intervention group. Some studies reported an absence of adverse events, 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

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 cointerventions, including complementary and alternative medicine therapies that have the potential to confound and contaminate study interventions

Comparator and Study Design

5. 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
6. Establish a sufficient sample size to evaluate potentially important confounders such as age, gender, and baseline severity
7. 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
8. Length of followup should be long enough to study medium- to long-term outcomes given the chronicity of tinnitus (e.g., the maximum length of followup in the

pharmacological/food supplement group of studies was 16 weeks, which is is inadequate to assess the durability of treatment over time)

Intervention

4. Establish a clear rationale for the dose used for off-label medications
5. Measure the concomitant use of co-interventions that have the potential to confound interventions (e.g., other pharmacological agents)
6. Specify the training and experience of the person(s) providing the interventions

Outcomes

7. Identify primary and secondary outcomes within the studies
8. Consider the inclusion of patient-reported outcomes using scales with established psychometric properties, including responsiveness, in the idiopathic tinnitus population
9. Assess the validity and responsiveness of outcome measurement instruments (e.g., VAS) in persons with tinnitus prior to using these instruments to evaluate the efficacy of tinnitus interventions
10. Ensure back translation of outcome measurement instruments prior to use in languages other than the language of development.
11. 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
12. Conform to the Consolidated Standards of Reporting Trials (CONSORT)[150] 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 trials may be required to capture harms adequately

Other

2. To 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 Consolidated Standards of Reporting Trials (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

Key Question 3

1. Studies should be developed to evaluate the natural history and prognostic factors in persons with subjective idiopathic tinnitus

References

1. American Tinnitus Association. Top 10 most frequently asked questions. www.ata.org/for-patients/faqs. Accessed:1-10-2011.

2. Davis A, El Rafaie A. Epidemiology of tinnitus. In: Epidemiology of tinnitus, Tyler RS,ed. San Diego,CA: Singular Publishing Group; 2000. 1 p. 1-24.

3. Press release: Two ATA Scientific Advisory Committee members receive Department of Defense grant. http://www.ata.org/about-ata/news-pubs/press-releases#DoDGrant. Accessed:6-1-2011.

4. Savage J, Cook S, Wadell A. Tinnitus. Clin Evid. 2007; PMID:19454115

5. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. Am J Med. 2010;123(8):711-8. PMID:20670725

6. Zoger S, Erlandsson S, Svedlund J, et al. Benefits from group psychotherapy in the treatment of severe refractory tinnitus. Audiol Med. 2008;6(1):62-72.

7. Scott B, Lindberg P, Lyttkens L, et al. Psychological treatment of tinnitus. Scand Audiol. 1985;14(4):223-30.

8. Weber C, Arck P, Mazurek B, et al. Impact of a relaxation training on psychometric and immunologic parameters in tinnitus sufferers. J Psychosom Res. 2002;52(1):29-33. PMID:11801262

9. Henry,J.A. 2011 Jul 26; Key informant interview.

10. Henry JA, Zaugg TL, Myers PJ, et al. A triage guide for tinnitus. J Fam Pract. 2010;59(7):389-93. PMID:20625568

11. Tinnitus: Guidelines for primary care. British Tinnitus Association. 2009; http://tinnitus.demonweb.co.uk/files/Tinnitus%20%20Guidelines%20for%20Primary%20Care.pdf. Accessed: 9-19-2012.

12. Holgers K-M. Mechanisms and classification of tinnitus: A discussion paper. Audiol Med. 2003;1(4):238-41.

13. Kroner-Herwig B, Frenzel A, Fritsche G, et al. The management of chronic tinnitus: Comparison of an outpatient cognitive-behavioral group training to minimal-contact interventions. J Psychosom Res. 2003;54(4):381-9. PMID:12670617

14. Weise C, Heinecke K, Rief W. Biofeedback-based behavioral treatment for chronic tinnitus: Results of a randomized controlled trial. J Consult Clin Psychol. 2008;76(6):1046-57. PMID:19045972

15. Dobie RA. A review of randomized clinical trials in tinnitus. Laryngoscope. 1999;109(8):1202-11. PMID:10443820

16. McCombe A, Baguley D, Coles R, et al. Guidelines for the grading of tinnitus severity: The results of a working group commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. Clin Otolaryngol Allied Sci. 2001;26(5):388-93. PMID:11678946

17. Erlandsson S. Psychological profiles of tinnitus in patients. In: Tinnitus Handbook, Tyler RS, ed. San Diego, CA: Singular Publishing Group; 2000. 2 p. 25-58.

18. Figueiredo RR, Azevedo AA, Oliveira PM. Correlation analysis of the visual-analogue scale and the Tinnitus Handicap Inventory in tinnitus patients. Revista Brasil Otorrinolaringol. 2009;75(1):76-9. PMID:19488564

19. Kamalski DM, Hoekstra CE, van Zanten BG, et al. Measuring disease-specific health-related quality of life to evaluate treatment outcomes in tinnitus patients: A systematic review. Otolaryngol Head Neck Surg. 2010;143(2):181-5.

20. Lipsey MW. Design sensitivity: Statistical power for experimental research. Newburry Park, CA: Sage Publications, Inc.; 1990.

21. Kazdin AE. Research design in clinical psychology. 4th. Needham Heights, MA: Allyn & Bacon; 2003.

22. Meikle M, Henry JA, Griest S, et al. The Tinnitus Functional Index: Development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear. 2011;32(5): PMID: 22156949

23. Baldo P, Doree C, Lazzarini R, et al. Antidepressants for patients with tinnitus. Cochrane Database Syst Rev. 2006;(4):CD003853. PMID:17054188

24. Johnson RM, Brummett R, Schleuning A. Use of alprazolam for relief of tinnitus. A double-blind study. Arch Otolaryngol Head Neck Surg. 1993;119(8):842-5. PMID:8343245

25. Jalali MM, Kousha A, Naghavi SE, et al. The effects of alprazolam on tinnitus: A cross-over randomized clinical trial. Med Sci Mon. 2009;15(11):I55-I60 PMID:19865063

26. Kalcioglu MT, Bayindir T, Erdem T, et al. Objective evaluation of the effects of intravenous lidocaine on tinnitus. Hear Res. 2005;199(1-2):81-8. PMID:15574302

27. Agarwal L, Pothier DD. Vasodilators and vasoactive substances for idiopathic sudden sensorineural hearing loss. Cochrane Database Syst Rev. 2009;(4):CD003422. PM:19821308

28. Noble W. Treatments for tinnitus. Trends Amplification. 2008;12(3):236-41. PMID:18635586

29. Sziklai I, Szilvassy J, Szilvassy Z. Tinnitus control by dopamine agonist pramipexole in presbycusis patients: A randomized, placebo-controlled, double-blind study. Laryngoscope. 2011;121(4):888-93. PMID:21433025

30. Hilton M, Stuart E. Ginkgo biloba for tinnitus. Cochrane Database Syst Rev. 2004;(2):CD003852. PMID:15106224

31. Teggi R, Bellini C, Piccioni LO, et al. Transmeatal low-level laser therapy for chronic tinnitus with cochlear dysfunction. Audiol Neuro Otol. 2009;14(2):115-20. PMID:18843180

32. Tuz HH, Onder EM, Kisnisci RS. Prevalence of otologic complaints in patients with temporomandibular disorder. Am J Orthod Dentofacial Orthop. 2003;123(6):620-3. PMID:12806339

33. Wright EF, Syms CA, III, Bifano SL. Tinnitus, dizziness, and nonotologic otalgia improvement through temporomandibular disorder therapy. Milit Med. 2000;165(10):733-6. PMID:11050868

34. Ash CM, Pinto OF. The TMJ and the middle ear: Structural and functional correlates for aural symptoms associated with temporomandibular joint dysfunction. Int J Prosthodont. 1991;4(1):51-7. PM:2012671

35. Langguth B, Hajak G, Kleinjung T, et al. Repetitive transcranial magnetic stimulation and chronic tinnitus. Acta Otolaryngol Suppl. 2006;(556):102-5. PMID:17114153

36. Henry JA, Dennis KC, Schechter MA. General review of tinnitus: Prevalence, mechanisms, effects, and management. J Speech Lang Hear Res. 2005;48(5):1204-35. PMID:16411806

37. Park J, White AR, Ernst E. Efficacy of acupuncture as a treatment for tinnitus: A systematic review. Arch Otolaryngol Head Neck Surg. 2000;126(4):489-92. PMID:10772302

38. Bennett M, Kertesz T, Yeung P. Hyperbaric oxygen therapy for idiopathic sudden sensorineural hearing loss and tinnitus: A systematic review of randomized controlled trials. J Laryngol Otol. 2005;119(10):791-8. PMID:16259656

39. Keate, B. Diet and tinnitus: What to eat . . . and what not to eat. Tinnitus Library. http://www.tinnitusformula.com/infocenter/articles/treatments/diet.aspx. http://www.tinnitusformula.com/infocenter/articles/treatments/diet.aspx. Accessed:6-10-2011.

40. Tinnitus and your diet. New Tinnitus Treatments Blog. 2011; http://www.tinnitustreatments.org/tinnitus-and-your-diet.html. Accessed: 6-10-2011.

41. Tinnitus relief through diet - Foods to avoid to relieve tinnitus. Tinnitus Remedies Web Site. 2011; http://www.thetinnitussite.info/tinnitus-relief-2/tinnitus-relief-through-diet-foods-to-avoid-to-relieve-tinnitus. Accessed: 6-10-2011.

42. Henry JA, Zaugg TL, Myers PJ, et al. Progressive audiologic tinnitus management. ASHA Leader. 2008;13(8):14-7.

43. Hobson J, Chisholm E, El RA. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst Rev. 2010;12:CD006371. PMID:21154366

44. CIGNA medical coverage policy No. 0220. Tinnitus treatment services and devices. http://www.cigna.com/assets/docs/health-care-professionals/coverage_positions/mm_0220_coveragepositioncriteria_tinnitus_instr_devices_retraining_ther.pdf. Accessed:6-10-2011.

45. Davis PB, Wilde RA, Steed LG, et al. Treatment of tinnitus with a customized acoustic neural stimulus: A controlled clinical study. Ear Nose Throat J. 2008;87(6):330-9. PMID:18561116

46. Davis PB, Paki B, Hanley PJ. Neuromonics tinnitus treatment: Third clinical trial. Ear Hear. 2007;28(2):242-59. PMID:17496674

47. Langguth B, Kleinjung T, Landgrebe M. Tinnitus: The complexity of standardization. Eval Health Prof. 2011;34(4):429-33. PMID:21224265

48. Martinez-Devesa P, Perera R, Theodoulou M, et al. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev. 2010;(9):CD005233. PMID:20824844

49. Department of Health. Provision of services for adults with tinnitus: A good practice guide. London: Central Office of Information; 2009.

50. Phillips JS, McFerran D. Tinnitus Retraining Therapy (TRT) for tinnitus. Cochrane Database Syst Rev. 2010;(3):CD007330. PMID:20238353

51. Jastreboff PJ, Hazell JW. A neurophysiological approach to tinnitus: Clinical implications. Br J Audiol. 1993;27(1):7-17. PMID:8339063

52. Ireland CE, Wilson PH, Tonkin JP, et al. An evaluation of relaxation training in the treatment of tinnitus. Behav Res Ther. 1985;23(4):423-30. PMID:3896227

53. Henry JA, Zaugg TL, Myers PJ, et al. The role of audiologic evaluation in progressive audiologic tinnitus management. Trends Amplification. 2008;12(3):170-87. PMID:18628281

54. Cima RF, Maes IH, Joore MA, et al. Specialised treatment based on cognitive behaviour therapy versus usual care for tinnitus: A randomised controlled trial. Lancet. 2012;379(9830):1951-9. PM:22633033

55. Davis A, Smith P, Ferguson M, et al. Acceptability, benefit and costs of early screening for hearing disability: A study of potential screening tests and models. Health Technol Assess. 2007;11(42):iii-294 PMID:17927921

56. Searchfield G. A commentary on the complexity of tinnitus management: Clinical guidelines provide a path through the fog. Eval Health Prof. 2011; PM:21224266

57. Hoare DJ, Gander PE, Collins L, et al. Management of tinnitus in English NHS audiology departments: An evaluation of current practice. J Eval Clin Pract. 2010; PM:21087449

58. Henry JA, Schechter MA, Loovis CL, et al. Clinical management of tinnitus using a "progressive intervention" approach. J Rehabil Res Dev. 2005;42(4:Suppl 2):95-116. PMID:16470467

59. Juni P, Holenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: Empirical study. Int J Epidemiol. 2002;31(1):115-23.

60. Moher D, Pham B, Klassen T, et al. What contributions do languages other than English make on the results of meta-analysis? J Clin Epidemiol. 2000;53(9):964-72.

61. Wells, G. A., Shea, B., O'Connell, D. et al. The Newcastle-Ottawa Scale (NOW) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed:9-19-2012. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

62. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17(1):1-12. PM:8721797

63. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207.

64. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol. 2011;64(12):1294-302. PM:21803546

65. Martinez DP, Perera R, Theodoulou M, et al. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev. 2010;(2):CD005233 PM:17253549

66. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-care program. J Clin Epidemiol. 2010;63(5):513-23. PM:19595577

67. Grading the strength of a body of evidence when assessing health care interventions: An update [Draft]. Rockville, MD: Agency for Healthcare Research and Quality; 2012.

68. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144(6):427-37. PM:16549855

69. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol. 2011;64(12):1277-82. PM:21802904

70. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64. PMID:19622511

71. Abbott JA, Kaldo V, Klein B, et al. A cluster randomised trial of an internet-based intervention program for tinnitus distress in an industrial setting. Cognit Behav Ther. 2009;38(3):162-73. PMID:19675959

72. Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: Double-blind study. Revista Brasil Otorrinolaringol. 2005;71(5):618-23. PMID:16612523

73. Anders M, Dvorakova J, Rathova L, et al. Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: A randomized, placebo controlled study. Neuroendocrinol Lett. 2010;31(2):238-49. PMID:20424590

74. Andersson G, Stromgren T, Strom L, et al. Randomized controlled trial of internet-based cognitive behavior therapy for distress associated with tinnitus. Psychosom Med. 2002;64(5):810-6. PMID:12271112

75. Andersson G, Porsaeus D, Wiklund M, et al. Treatment of tinnitus in the elderly: A controlled trial of cognitive behavior therapy. Int J Audiol. 2005;44(11):671-5. PMID:16379495

76. Aoki M, Wakaoka Y, Hayashi H, et al. Effect of lyophilized powder made from enzymolyzed honeybee larvae on tinnitus-related symptoms, hearing levels, and hypothalamus-pituitary-adrenal axis-related hormones. Ear Hear. 2012;33(3):430-6. PMID:21971082

77. Arda HN, Tuncel U, Akdogan O, et al. The role of zinc in the treatment of tinnitus. Otol Neurotol. 2003;24(1):86-9. PMID:12544035

78. Biesinger E, Kipman U, Schatz S, et al. Qigong for the treatment of tinnitus: A prospective randomized controlled study. J Psychosom Res. 2010;69(3):299-304. PMID:20708452

79. Chung HK, Tsai CH, Lin YC, et al. Effectiveness of theta-burst repetitive transcranial magnetic stimulation for treating chronic tinnitus. Audiol Neuro Otol. 2012;17(2):112-20. PMID:21865723

80. Cuda D, De CA. Effectiveness of combined counseling and low-level laser stimulation in the treatment of disturbing chronic tinnitus. Int Tinnitus J. 2008;14(2):175-80. PMID:19205171

81. Dib GC, Kasse CA, Alves de AT, et al. Tinnitus treatment with Trazodone. Revista Brasil Otorrinolaringol. 2007;73(3):390-7. PMID:17684661

82. Dineen R, Doyle J, Bench J. Managing tinnitus: A comparison of different approaches to tinnitus management training. Br J Audiol. 1997;31(5):331-44. PMID:9373742

83. Dineen R, Doyle J, Bench J, et al. The influence of training on tinnitus perception: An evaluation 12 months after tinnitus management training. Br J Audiol. 1999;33(1):29-51. PMID:10219721

84. Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: Double blind, placebo controlled trial. BMJ. 2001;322(7278):73 PMID:11154618

85. Ghossaini SN, Spitzer JB, Mackins CC, et al. High-frequency pulsed electromagnetic energy in tinnitus treatment. Laryngoscope. 2004;114(3):495-500. PMID:15091224

86. Henry JL, Wilson PH. The psychological management of tinnitus: Comparison of a combined cognitive educational program, education alone and a waiting list control. Int Tinnitus J. 1996;2:9-20.

87. Henry JL, Wilson PH. An evaluation of two types of cognitive intervention in the management of chronic tinnitus. Scand J Behav Ther. 1998;27(4):156-66.

88. Henry JA, Loovis C, Montero M, et al. Randomized clinical trial: Group counseling based on tinnitus retraining therapy. J Rehabil Res Dev. 2007;44(1):21-32. PMID:17551855

89. Hiller W, Haerkotter C. Does sound stimulation have additive effects on cognitive-behavioral treatment of chronic tinnitus? Behav Res Ther. 2005;43(5):595-612. PMID:15865915

90. Holgers K-M, Zoger S, Svedlund J. The impact of sertraline on health-related quality of life in severe refractory tinnitus: A double-blind, randomized, placebo-controlled study. Audiol Med. 2011;9(2):67-72.

91. Kaldo V, Cars S, Rahnert M, et al. Use of a self-help book with weekly therapist contact to reduce tinnitus distress: A randomized controlled trial. J Psychosom Res. 2007;63(2):195-202. PMID:17662757

92. Kaldo V, Levin S, Widarsson J, et al. Internet versus group cognitive-behavioral treatment of distress associated with tinnitus: A randomized controlled trial. Behav Ther. 2008;39(4):348-59. PMID:19027431

93. Kroner-Herwig B, Hebing G, van Rijn-Kalkmann U, et al. The management of chronic tinnitus--Comparison of a cognitive-behavioural group training with yoga. J Psychosom Res. 1995;39(2):153-65. PMID:7595873

94. Langguth B, Kleinjung T, Frank E, et al. High-frequency priming stimulation does not enhance the effect of low-frequency rTMS in the treatment of tinnitus. Exp Brain Res. 2008;184(4):587-91. PMID:18066684

95. Malouff JM, Noble W, Schutte NS, et al. The effectiveness of bibliotherapy in alleviating tinnitus-related distress. J Psychosom Res. 2010;68(3):245-51. PMID:20159209

96. Marcondes RA, Sanchez TG, Kii MA, et al. Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: A double-blind controlled, clinical and neuroimaging outcome study. Eur J Neurol. 2010;17(1):38-44. PMID:19614962

97. Mazurek B, Haupt H, Szczepek AJ, et al. Evaluation of vardenafil for the treatment of subjective tinnitus: A controlled pilot study. J Negative Results Biomed. 2009;8:3. PMID:19222841

98. Meeus O, De RD, Van de Heyning P. Administration of the combination clonazepam-Deanxit as treatment for tinnitus. Otol Neurotol. 2011;32(4):701-9. PMID:21358561

99. Mirz F, Zachariae R, Andersen SE, et al. The low-power laser in the treatment of tinnitus. Clin Otolaryngol Allied Sci. 1999;24(4):346-54. PMID:10472473

100. Parazzini M, Del B, Jastreboff M, et al. Open ear hearing aids in tinnitus therapy: An efficacy comparison with sound generators. Int J Audiol. 2011;50(8):548-53. http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=2011208063&site=ehost-live;Publisher URL: www.cinahl.com/cgi-bin/refsvc?jid=2576&accno=2011208063

101. Piccirillo JF, Finnell J, Vlahiotis A, et al. Relief of idiopathic subjective tinnitus: Is gabapentin effective? Arch Otolaryngol Head Neck Surg. 2007;133(4):390-7. PMID:17438255

102. Plewnia C, Vonthein R, Wasserka B, et al. Treatment of chronic tinnitus with theta burst stimulation: A randomized controlled trial. Neurology. 2012;78(21):1628-34. PMID:22539568

103. Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: A randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. Clin Otolaryngol Allied Sci. 2004;29(3):226-31. PMID:15142066

104. Rief W, Weise C, Kley N, et al. Psychophysiologic treatment of chronic tinnitus: A randomized clinical trial. Psychosom Med. 2005;67(5):833-8. PMID:16204446

105. Robinson SK, Viirre ES, Bailey KA, et al. Randomized placebo-controlled trial of a selective serotonin reuptake inhibitor in the treatment of nondepressed tinnitus subjects. Psychosom Med. 2005;67(6):981-8. PMID:16314604

106. Sharma DK, Kaur S, Singh J, et al. Role of acamprosate in sensorineural tinnitus. Indian J Pharmacol. 2012;44(1):93-6.

107. Sullivan M, Katon W, Russo J, et al. A randomized trial of nortriptyline for severe chronic tinnitus. Effects on depression, disability, and tinnitus symptoms. Arch Intern Med. 1993;153(19):2251-9. PMID:8215728

108. Tass PA, Adamchic I, Freund H-J, et al. Counteracting tinnitus by acoustic coordinated reset neuromodulation. Restor Neurol Neurosci. 2012;30(2):137-59.

109. Topak M, Sahin-Yilmaz A, Ozdoganoglu T, et al. Intratympanic methylprednisolone injections for subjective tinnitus. J Laryngol Otol. 2009;123(11):1221-5. PMID:19640315

110. Vilholm OJ, Moller K, Jorgensen K. Effect of traditional Chinese acupuncture on severe tinnitus: A double-blind, placebo-controlled, clinical investigation with open therapeutic control. Br J Audiol. 1998;32(3):197-204. PMID:9710337

111. Westerberg BD, Roberson JB, Jr., Stach BA. A double-blind placebo-controlled trial of baclofen in the treatment of tinnitus. Am J Otol. 1996;17(6):896-903. PMID:8915419

112. Westin VZ, Schulin M, Hesser H, et al. Acceptance and commitment therapy versus tinnitus retraining therapy in the treatment of tinnitus: A randomised controlled trial. Behav Res Ther. 2011;49(11):737-47. PMID:21864830

113. Zachriat C, Kroner-Herwig B. Treating chronic tinnitus: Comparison of cognitive-behavioural and habituation-based treatments. Cognit Behav Ther. 2004;33(4):187-98. PMID:15625793

114. Zoger S, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering--A randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2006;26(1):32-9. PMID:16415703

115. Neri G, De SA, Baffa C, et al. Treatment of central and sensorineural tinnitus with orally administered Melatonin and Sulodexide: Personal experience from a randomized controlled study. Acta Otorhinolaryngol Ital. 2009;29(2):86-91. PMID:20111618

116. Figueiredo RR, Langguth B, Mello de OP, et al. Tinnitus treatment with memantine. Otolaryngol Head Neck Surg. 2008;138(4):492-6. PMID:18359360

117. Akkuzu B, Yilmaz I, Cakmak O, et al. Efficacy of misoprostol in the treatment of tinnitus in patients with diabetes and/or hypertension. Auris Nasus Larynx. 2004;31(3):226-32. PMID:15364356

118. Bayar N, Boke B, Turan E, et al. Efficacy of amitriptyline in the treatment of subjective tinnitus. J Otolaryngol. 2001;30(5):300-3. PMID:11771024

119. Dobie RA, Sakai CS, Sullivan MD, et al. Antidepressant treatment of tinnitus patients: Report of a randomized clinical trial and clinical prediction of benefit. Am J Otol. 1993;14(1):18-23. PMID:8424470

120. Suckfüll M, Althaus M, Ellers-Lenz B, et al. A randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of neramexane in patients with moderate to severe subjective tinnitus. BMC Ear Nose Throat Disord. 2011;11(1):

121. Dehkordi MA, Abolbashari S, Taheri R, et al. Efficacy of gabapentin on subjective idiopathic tinnitus: A randomized, double-blind, placebo-controlled trial. Ear Nose Throat J. 2011;90(4):

122. Jakes SC, Hallam RS, McKenna L, et al. Group cognitive therapy for medical patients: An application to tinnitus. Cognit Ther Res. 1992;Vol16, pp67-82, 1992:67-82.

123. Herraiz C, Diges I, Cobo P, et al. Auditory discrimination training for tinnitus treatment: The effect of different paradigms. Eur Arch Otorhinolaryngol. 2010;267(7):1067-74. PMID:20044759

124. Olzowy B, Canis M, Hempel JM, et al. Effect of atorvastatin on progression of sensorineural hearing loss and tinnitus in the elderly: Results of a prospective, randomized, double-blind clinical trial. Otol Neurotol. 2007;28(4):455-8. PMID:17529847

125. Searchfield GD, Kaur M, Martin WH. Hearing aids as an adjunct to counseling: Tinnitus patients who choose amplification do better than those that don't. Int J Audiol. 2010;49(8):574-9. PMID:20500032

126. Mason JD, Rogerson DR, Butler JD. Client centred hypnotherapy in the management of tinnitus--Is it better than counselling? J Laryngol Otol. 1996;110(2):117-20. PMID:8729491

127. Pandey S, Mahato NK, Navale R. Role of self-induced sound therapy: Bhramari Pranayama in Tinnitus. Audiol Med. 2010;8(3):137-41.

128. Erlandsson SI, Rubinstein B, Carlsson SG. Tinnitus: Evaluation of biofeedback and stomatognathic treatment. Br J Audiol. 1991;25(3):151-61. PMID:1873582

129. Bonaconsa A, Mazzoli MM, Antonia M, et al. Posturography measures and efficacy of different physical treatments in somatic tinnitus. Int Tinnitus J. 2010;16(1):44-50. PMID:21609913

130. Neri G, Baffa C, De SA, et al. Management of tinnitus: Oral treatment with melatonin and sulodexide. Journal of Biological Regulators & Homeostatic Agents. 2009;23(2):103-10. PMID:19589291

131. Lindberg P, Scott B, Melin L, et al. The psychological treatment of tinnitus: An experimental evaluation. Behav Res Ther. 1989;27(6):593-603. PMID:2692553

132. Gungor A, Dogru S, Cincik H, et al. Effectiveness of transmeatal low power laser irradiation for chronic tinnitus. J Laryngol Otol. 2008;122(5):447-51. PMID:17625032

133. Roland NJ, Hughes JB, Daley MB, et al. Electromagnetic stimulation as a treatment of tinnitus: A pilot study. Clin Otolaryngol Allied Sci. 1993;18(4):278-81. PMID:8877185

134. Khedr EM, Rothwell JC, Ahmed MA, et al. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: Comparison of different stimulus frequencies. J Neurol Neurosurg Psychiatry. 2008;79(2):212-5. PMID:18202212

135. Podoshin L, Ben-David Y, Fradis M, et al. Idiopathic subjective tinnitus treated by biofeedback, acupuncture and drug therapy. Ear Nose Throat J. 1991;70(5):284-9. PMID:1914952

136. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: Framework for a structured approach. BMC Med Res Methodol. 2007;7:32. PM:17615054

137. Montori VM, Guyatt GH. Intention-to-treat principle. CMAJ. 2001;165(10):1339-41. PM:11760981

138. Klockhoff I, Lindblom U. Meniere's disease and hydrochlorothiazide (Dichlotride)--A critical analysis of symptoms and therapeutic effects. Acta Otolaryngol. 1967;63(4):347-65. PMID:6033658

139. Geyh S, Cieza A, Schouten J, et al. ICF Core Sets for stroke. J Rehabil Med. 2004;(44 Suppl):135-41. PM:15370761

140. Meng Z, Liu S, Zheng Y, et al. Repetitive transcranial magnetic stimulation for tinnitus. Cochrane Database Syst Rev. 2011;(10):CD007946 PMID:21975776

141. Savage J, Waddell A. Tinnitus. Clinical Evidence. 2012;2012,2012 PMID:22331367

142. Hoare DJ, Kowalkowski VL, Kang S, et al. Systematic review and meta-analyses of randomized controlled trials examining tinnitus management. Laryngoscope. 2011;121(7):1555-64. PMID:21671234

143. Hesser H, Weise C, Westin VZ, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive-behavioral therapy for tinnitus distress. Clinical Psychology Review. 2011;31(4):545-53. PMID:21237544

144. Kochkin S, Tyler R, Born J. MarkeTrak VIII: The prevalence of tinnitus in the United States and the self-reported efficacy of various treatments. Hear Rev. 2011;18(12):10-27.

145. Nondahl DM, Cruickshanks KJ, Huang GH, et al. Generational differences in the reporting of tinnitus. Ear Hear. 2012;33(5):640-4. PM:22588269

146. Hoekstra CE, Rynja SP, van Zanten GA, et al. Anticonvulsants for tinnitus. Cochrane Database Syst Rev. 2011;(7):CD007960. PMID:21735419

147. Karkos PD, Leong SC, Arya AK, et al. 'Complementary ENT': A systematic review of commonly used supplements. J Laryngol Otol. 2007;121(8):779-82. PMID:17125579

148. Hilton, Malcolm P, Stuart, et al. Ginkgo biloba for tinnitus. Cochrane Database Syst Rev. 2010;(3):

149. Baldo, Paolo, Doree, et al. Antidepressants for patients with tinnitus. Cochrane Database Syst Rev. 2009;(1):

150. Ioannidis JPA, Evans SJW, Gotzsche PC, et al. Better reporting of harms in randomized trials: An extension of the CONSORT statement. Ann Intern Med. 2004;141(10):781-8.