Comparative Effectiveness Review
Number 122

Effective Health Care Program

Evaluation and Treatment of Tinnitus: Comparative Effectiveness

Executive Summary

Background

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

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

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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

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of intervention: pharmacological or food supplement, medical/surgical, sound technology, and psychological/behavioral.

Scope and Key Questions

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

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

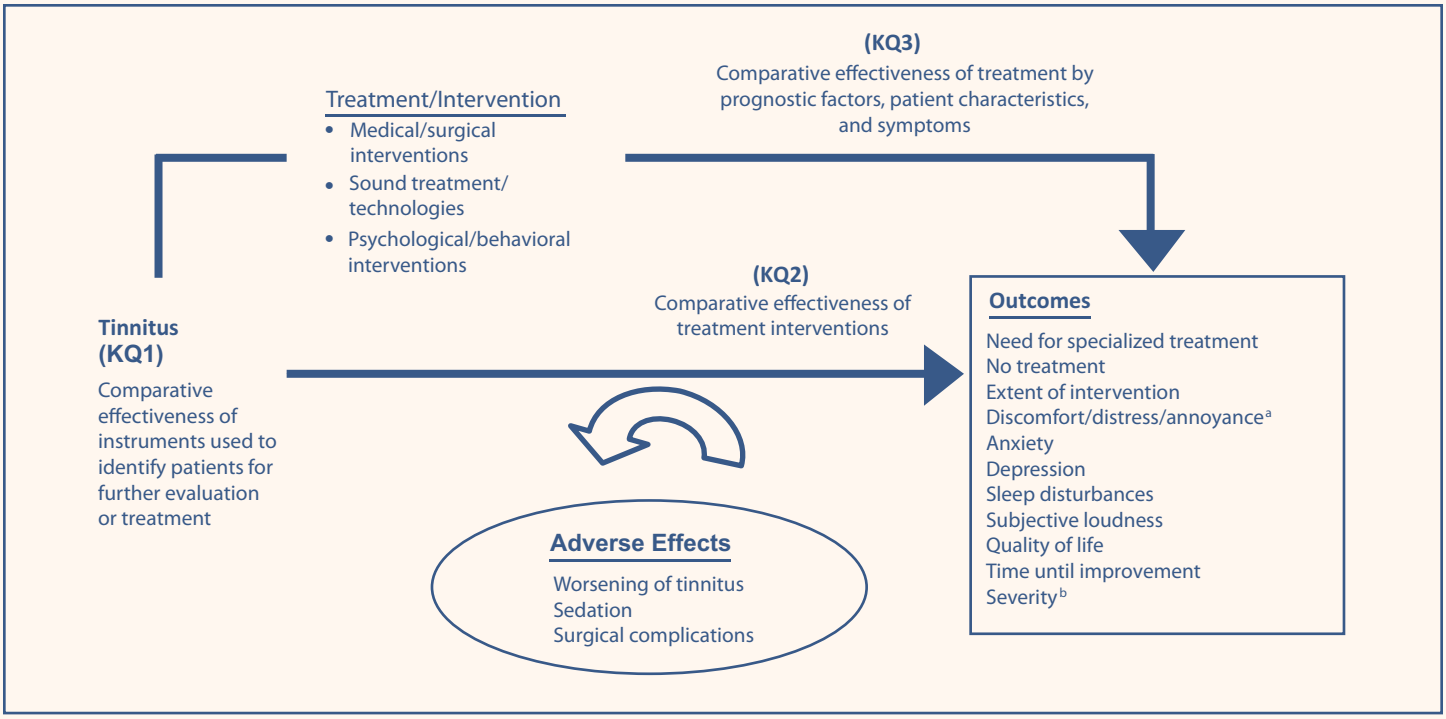
KQ2. In adults with subjective idiopathic (nonpulsatile) tinnitus, what is the comparative effectiveness (and/or potential harms) of medical/surgical, sound treatment/technological, or psychological/behavioral interventions, including combinations of interventions?

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

Analytic Framework

Following consultation with Key Informants, the Agency for Healthcare Research and Quality (AHRQ) Task Order Officer, and the investigative team, key research questions were developed. Figure A shows a flow diagram indicating the relationship between research questions in this comparative effectiveness review (CER). This framework depicts the KQ as outlined in the PICOTS (population(s), interventions, comparators, outcomes, timing or followup, and setting) format. The PICOTS components for each KQ are provided in full detail in Table A.

Figure A. Analytic framework



KQ = Key Question

[a]Any studies that used the terms "annoyance" or "distress" to describe their outcomes were included under the category of "discomfort."

[b]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

Search Strategy

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

Criteria for Inclusion/Exclusion of Studies in the Review

Included studies had to be randomized controlled trials (RCTs) or observational studies with true control groups (e.g., cohort, case control). For KQ2 and KQ3, included studies had to evaluate tinnitus treatments. Studies were excluded when tinnitus resulted from middle-ear pathologies (mechanics, otitis media, otosclerosis, etc.), when interventions were stapedectomy or tympanoplasty, or when interventions were focused on determining whether patients had psychosomatic tinnitus. See Table A for inclusion and exclusion criteria.

Data Extraction, Assessment of Risk of Bias, and Applicability

Standardized and validated scales were used (the Newcastle-Ottawa quality assessment scales for case-control studies and cohort studies,[7] and the Jadad scale for RCTs[8]) to assess risk of bias. Two raters evaluated the studies using standardized assessment forms, and disagreements were resolved through consensus. Applicability[9] was assessed by considering comorbidities (psychological or related to hearing loss), ages of subjects, locations where study subjects were recruited, specific treatment providers, and lengths of time to treatment.

Data Synthesis and Strength of Evidence

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

Table A. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	**KQ1**: Adult (≥18 years) patients who visit health care practitioners with symptoms of tinnitus (ringing in the ears, whooshing sounds, etc.) **KQ2 & KQ3**: Adults (≥18 years) with a diagnosis of subjective idiopathic (nonpulsatile) tinnitus who are sufficiently bothered by tinnitus that they are seeking a treatment intervention No restriction on the length of time of symptoms	•Subjects <18 years of age •Dx of pulsatile tinnitus •Unilateral cases with specific medical dx (e.g., paraganglioma, acoustic neuroma) •Tinnitus as side effect of drugs •Nonhuman

Table A. Inclusion and exclusion criteria (continued)		
Category	**Inclusion Criteria**	**Exclusion Criteria**
Interventions	**KQ1**: Direct observation or observation of sound with stethoscope; referral to a health professional with expertise on managing tinnitus (i.e., otolaryngologist, audiologist, neurologist, mental health professional); administration of scales/questionnaires to assess severity (THI, TRQ, TSI, VAS, etc.) **KQ2**: Any treatment/therapy used to reduce/help cope with tinnitus, including but not limited to the following: **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 • Hyperbaric oxygen therapy • Complementary and alternative medicine therapies: Gingko biloba extracts; acupuncture; diet, lifestyle, and sleep modifications (caffeine avoidance, exercise) **Sound Treatments/Technologies** • Hearing aids, cochlear implants, sound generators, maskers • Neuromonics **Psychological/Behavioral** • Cognitive behavioral therapy, biofeedback, education, relaxation therapies, Progressive Tinnitus Management, tinnitus retraining therapy **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**: Nondirect observations **KQ2**: No exclusions for interventions **KQ3**: No exclusions for interventions

Table A. Inclusion and exclusion criteria (continued)		
Category	**Inclusion Criteria**	**Exclusion Criteria**
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 symptoms, depression symptoms, subjective loudness, quality of life, return to "normal" work, adverse effects (worsening of tinnitus, sedation, surgical complications)	No exclusions
Publication language	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 providing sufficient detail about methods and results to enable use and aggregation of the data and results **All KQs**: Possibility of extracting relevant outcomes 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, abstracts, and Webcasts
Setting	**All KQs**: Primary care, specialty care (audiology, otolaryngology, neurology, mental health), university research, Internet	No exclusions

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

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

Peer Review and Public Comment

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

Results

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

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

No studies were found to address this KQ.

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

Pharmacological or Food Supplement Interventions

A total of 17 articles[12-28] reported on 16 unique studies that evaluated interventions in the pharmacological or food supplement domain (Table B). Five articles[12-16] investigated antidepressant drugs versus placebo. These drugs included sertraline,[12,13] paroxetine,[14] trazodone,[15] and nortriptyline.[16] Dosage levels in the sertraline, paroxetine, and nortriptyline articles were at the recommended levels for treating depression. However, the dosage level in the trazodone study was below the recommended dose for depression; the dosage level was instead suitable for use as a sleep aid. Five publications[17-21] examined neurotransmitter drugs, which stimulate or enhance γ-aminobutyric acid (GABA), versus placebo. The neurotransmitter drugs were gabapentin,[17] baclofen,[18] alprazolam,[19] and acamprosate.[20,21] Three studies investigated other drugs, including methylprednisolone versus placebo,[22] vardenafil versus placebo,[23] and Deanxit versus placebo (with each participant given 1 mg clonazepam in addition to Deanxit or placebo).[24] Four papers evaluated food supplements, with two[25,26] focused on Gingko biloba, one[27] on zinc, and one28 on honeybee larvae. All food supplements were compared with placebo (which was hydrogenated dextrin in the larvae study). All of the studies were RCTs.

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

Table B. Summary of findings for Key Question 2: Pharmacological or food supplement interventions			
Outcome	**# of Articles**	**Overall Strength of Evidence**	**Comment**
Tinnitus-specific quality of life	13[12-14,16-18,21-26,28]	Insufficient for antidepressants, neurotransmitter drugs, food supplements, and other drugs	Although nortriptyline, sertraline, acamprosate, and Deanxit were shown to produce some improvement in tinnitus-specific quality of life, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of moderate risk of bias and inconsistent and imprecise effect estimates.
Subjective loudness	9[12,13,18-20,22,24,26,27]	Low for neurotransmitter drugs Insufficient for antidepressants, food supplements, and other drugs	Evidence suggests that neurotransmitter drugs showed improvement in subjective loudness vs. placebo; however, because of moderate risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome. Only single studies of Deanxit, methylprednisolone, zinc, Gingko biloba, and sertraline showed improvements in subjective loudness compared with placebo. Based on single studies of each comparison, there is insufficient evidence to determine whether these findings represent true effects.
Sleep disturbance	3[14,23,24]	Insufficient for antidepressants and other drugs	The strength of evidence is insufficient to conclude whether paroxetine, vardenafil, and Deanxit showed improvements in subjective loudness compared with placebo. Only single studies of paroxetine and vardenafil reported improvements in sleep disturbance vs. placebo, and no improvement was observed with Deanxit. Based on single studies of each comparison, there is insufficient evidence to determine whether these findings represent true effects.
Anxiety symptoms	4[12-14,16]	Insufficient for antidepressants	The strength of evidence is insufficient to conclude whether sertraline, paroxetine, and nortriptyline showed improvements in anxiety symptoms compared with placebo. Only single studies comparing sertraline, paroxetine, or nortriptyline with placebo reported improvements in anxiety symptoms, with differences statistically significant only for sertraline. Based on single studies of each comparison, insufficient evidence exists to conclude whether these findings represent true effects

Table B. Summary of findings for Key Question 2: Pharmacological or food supplement interventions (continued)			
Outcome	**# of Articles**	**Overall Strength of Evidence**	**Comment**
Depression symptoms	6[12-14,16,24,28]	Insufficient for antidepressants, food supplements, and other drugs	The strength of evidence is insufficient to conclude whether sertraline, paroxetine, nortriptyline, honeybee larvae, and Deanxit showed improvements in depression symptoms compared with placebo. Although studies of sertraline, paroxetine, and nortriptyline reported improvements in depression symptoms vs. placebo, not all differences were statistically significant, the risk of bias was moderate, and effects were inconsistent. Only single studies evaluated Deanxit and honeybee larvae. Based on single studies for each of these interventions, insufficient evidence exists to conclude whether these findings represent true effects.
Global quality of life	6 (2 papers from the same study addressed sertraline)1[2-15,20,23,25]	Insufficient for antidepressants, food supplements, and other drugs	The strength of evidence is insufficient to conclude whether sertraline, paroxetine, trazodone, acamprosate, vardenafil, and Ginkgo biloba showed improvements in global quality of life compared with placebo. Although sertraline showed improved global quality of life vs. placebo, the evidence is insufficient to conclude whether the findings represent true effects because of moderate risk of bias, and inconsistent and imprecise effect estimates. Only single studies evaluated acamprosate, vardenafil, and Ginkgo biloba. Based on single studies for each of these interventions, insufficient evidence exists to conclude whether these findings represent true effects.

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

Medical Interventions

Eleven studies were included for medical interventions in KQ2 (Table C). Six[29-34] of these evaluated repetitive transcranial magnetic stimulation (rTMS) or electromagnetic stimulation; three evaluated low-level laser therapy (LLLT);[35-37] and one each evaluated acupuncture[38] and acoustic coordinated reset neuromodulation (ACRN) therapy.[39] All the studies in the medical intervention group have small sample sizes (n<60).

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

Table C. Summary of findings for Key Question 2: Medical interventions			
Outcome	**# of Articles**	**Overall Strength of Evidence**	**Comment**
Tinnitus-specific quality of life	9[29,30,32,33,35-39]	Insufficient for all interventions	Although most interventions showed no differences relative to placebo, the overall strength of evidence was insufficient because of high risk of bias and inconsistent and imprecise effect estimates. Only single studies evaluated high-frequency electromagnetic energy, ACRN, and acupuncture. Based on single studies for each of these interventions, there is insufficient evidence to conclude whether these findings represent true effects.
Subjective loudness	4[35,36,38,39]	Insufficient for LLLT, ACRN, and acupuncture	Although interventions showed no differences between treatment and placebo groups, the overall strength of evidence was insufficient because of high risk of bias and imprecise effect estimates. Only single studies evaluated high-frequency electromagnetic energy, ACRN, and acupuncture. Based on single studies for each of these interventions, there is insufficient evidence to conclude whether these findings represent true effects.
Sleep disturbance	0	Not applicable	No studies evaluated this outcome.
Anxiety symptoms	1[36]	Insufficient for LLLT	A single study with high risk of bias and small sample size compared laser therapy vs. sham; it showed that laser therapy had greater reduction in anxiety symptoms ($p > 0.05$). The strength of evidence is insufficient to conclude whether these findings represent true effects.
Depression symptoms	1[36]	Insufficient for LLLT	A single study with high risk of bias and small sample size compared laser therapy vs. sham; it showed that laser therapy had greater reduction in depression symptoms ($p > 0.05$). The strength of evidence is insufficient to conclude whether these findings represent true effects.
Global quality of life	0	Not applicable	No studies evaluated this outcome.

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

Sound Technology Interventions

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

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

Table D. Summary of findings for Key Question 2: Sound technology interventions			
Outcome	**# of Articles**	**Overall Strength of Evidence**	**Comment**
Tinnitus-specific quality of life	4[40-43]	Insufficient	There were no statistically significant differences between treatments in any of the studies, although benefits were reported for hearing aids, sound generators, and Neuromonics. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates.
Subjective loudness	3[41-43]	Insufficient	There were no statistically significant differences between treatments in any of the studies, although benefits were reported for both hearing aids and sound generators. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates.
Sleep disturbance	0	Not applicable	Not applicable.
Anxiety symptoms	1[41]	Insufficient	All groups in the study demonstrated improvement, but adding a noise generator to tinnitus education or cognitive behavioral therapy did not increase treatment benefits. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates of unknown consistency.
Depression symptoms	1[41]	Insufficient	A single study with high risk of bias showed no benefit from cognitive behavioral therapy with or without noise generation.
Global quality of life	3[41-43]	Insufficient	Benefit was reported for all interventions involving hearing aids or sound generators, but there were no differences depending on the technology used.[43] No benefits were reported for any other interventions. However, the overall strength of evidence is insufficient to conclude whether these findings represent true effects because of high risk of bias and imprecise estimates.

Psychological and Behavioral Interventions

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

Adverse effects were not consistently reported or specified in the methods of the studies. None of the studies in the psychological and behavioral interventions group reported dropouts related to adverse effects. Eight studies clearly stated there were no adverse effects reported.[45-49,52,60,61] One study[62] reported an increase in negative effects (loudness of and discomfort from their tinnitus) from intensive self-monitoring.

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

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

Table E. Summary of findings for Key Question 2: Psychological and behavioral interventions (continued)			
Outcome	**# of Articles**	**Overall Strength of Evidence**	**Comment**
Anxiety symptoms	5[51,53,56,60,63]	Low evidence of no effect for CBT	Although treatment benefits were shown for 1 intervention (self-help book + telephone therapy), overall, consistent evidence suggests that there was no effect for CBT on anxiety symptoms. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome.
		Insufficient for TRT and relaxation	Only single studies with high risk of bias evaluated TRT and relaxation.
Depression symptoms	11[49,51,53,55-60,62,63]	Low evidence of no effect for CBT	Although there are some treatment benefits with various forms of CBT, as well as an intervention involving relaxation and distraction, overall, consistent evidence suggests that there was no effect for CBT on depression symptoms. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome.
		Insufficient for TRT and relaxation	The strength of evidence is insufficient to conclude whether relaxation or TRT showed improvement in depression symptoms because of high risk of bias, imprecise and inconsistent estimates, or only single studies for some interventions in this outcome category.
Global quality of life	6[47,49,52,55,59,60]	Low evidence of no effect for CBT	Although there are some treatment benefits for biofeedback-based CBT and bibliotherapy, overall, consistent evidence suggests that there was no effect for CBT on global quality of life. However, because of high risk of bias and imprecise effect estimates, confidence is low that these findings lie close to the true effects for this outcome.
		Insufficient for TRT and other interventions	Only single studies with high risk of bias evaluated TRT and other interventions.

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

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

No studies were found to address this KQ.

Discussion and Conclusions

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

When considering the applicability of study findings in general, the study populations were relatively homogeneous and were limited to predominately middle-aged (≥50 years of age) persons suffering from subjective idiopathic tinnitus of mild to moderate severity. Of course, hearing loss also increases markedly with age starting in the fourth decade, and hearing loss and tinnitus often co-occur.[3] Nevertheless, tinnitus is a problem not only for older adults or for people with clinically significant hearing loss. A recent survey estimated that tinnitus was prevalent in 12.2 percent of the U.S. population under 44 years of age.[14,64] However, there is little evidence on which to draw conclusions about the efficacy of the therapies in persons younger than 42 years of age. Importantly, there may also be generational differences in the experience of tinnitus based on recent epidemiological research on adults over the age of 45 years.[4] The finding of generational differences suggests that reports of tinnitus tend to increase with more recent birth cohorts compared with earlier birth cohorts. Researchers should explore age and cohort differences as programs to treat, and possibly even programs to prevent, tinnitus continue to be developed and evaluated.

Tinnitus is a chronic condition. The longest followups in the included studies did not exceed 16 weeks in pharmacological and food supplement studies and 26 weeks in medical interventions. However, followup was extended to 12 months in all of the studies evaluating sound-based treatments[40,42,43] and even to 18 months for one study.[41] For the psychological and behavioral interventions, many studies evaluated the effectiveness of treatment immediately after treatment, as well as at one or more later followups (up to 18 months[60]). Thus, for the pharmacological and medical intervention categories, the included studies did not provide data on the medium- to long-term effects of the active treatments.

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

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

Key Findings and Strength of Evidence

Pharmacological or Food Supplement Interventions

A total of 16 unique studies (17 publications)[12-28] evaluated the efficacy of pharmacological interventions or food supplements in tinnitus. The included articles evaluated 14 different interventions, all of which were compared with some form of placebo. For the most part, the interventions failed to demonstrate statistically significant effects compared with placebo on any of the outcomes. Various interventions showed statistically significant effects on some outcomes: nortriptyline[16] and

honeybee larvae[28] for depression; alprazolam[19] and zinc[27] for loudness; and acamprosate[21] for tinnitus-specific quality of life (TSQoL) measured as "disturbance." One study[16] found conflicting results for TSQoL (e.g., improved TSQoL or no difference compared with placebo), depending on the instrument used to measure the outcome.

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

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

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

Medical Interventions

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

When considering the individual types of interventions and efficacy with respect to TSQoL, the studies consistently showed no significant difference between treatment and inactive comparators. For rTMS and electromagnetic stimulation, the evidence was rated as insufficient. There was some evidence that longer term effects (improvement in TSQoL scores) occurred with low-frequency rTMS (1 Hz) at up to 6 months followup,[29] but this single study had high risk of bias. Our review also showed that adverse effects were generally poorly evaluated and reported. A previous systematic review[71] reached similar conclusions, suggesting that the evidence of benefit for rTMS is limited, and also noted the lack of long-term monitoring within the studies with respect to safety.

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

Only five trials evaluated the outcome of perceived loudness,[32,35,36,38,39] and most trials showed no statistical differences between treatment and inactive control groups; however, the studies had small sample sizes and high risk of bias. SOE was rated as insufficient. One intervention (ACRN) showed small differences for one stimulation parameter compared with sham stimulation.[39] However, due to the added problem of the diversity of the medical interventions that evaluated this outcome, we rate the SOE as insufficient for all of these interventions.

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

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

Sound Technology Interventions

Four unique RCTs[40-43] and a related study[44] were eligible for this intervention category. Two of the studies[41,44] evaluated the relative effectiveness of various sound-based interventions to determine whether benefits were enhanced when sound generators were combined with CBT, information, or relaxation therapies. Half of the studies reported some benefits from sound generation, but none demonstrated any statistically significant differences

relative to comparator therapies. Two recent systematic reviews that evaluated different sets of eligible studies found similar results. The authors of these reviews discussed the diversity of interventions[66] in this domain and felt the evidence was insufficient to draw conclusions about the effectiveness of any therapies.[65,66]

Psychological and Behavioral Interventions

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

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

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

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

Future Research Recommendations

Key Question 1

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

Key Question 2

Population

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

Comparator and Study Design

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

Intervention

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

Outcomes

- Identify outcomes as primary or secondary.
- Use scales with established psychometric properties in populations with subjective idiopathic tinnitus to measure patient-reported outcomes.
- Assess the responsiveness to change of outcome measurement instruments (e.g., visual analog scale) in persons with tinnitus.
- Back-translate scales prior to use in languages other than the language in which they were developed.

- Measure global quality of life to capture how persons value the risk-benefit tradeoff between efficacy and adverse effects.
- Use the Consolidated Standards of Reporting Trials (CONSORT)[74] guidelines for reporting adverse effects (harms).

Other

- Report RCT results in conformity with CONSORT.[74]
- Register study protocols in clinical trial registries and update trial information in these registries regularly.

Key Question 3

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

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Full Report

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

AHRQ Pub. No. 13-EHC110-1-EF
August 2013