Evidence-based Practice Center Systematic Review Protocol

Project Title: Evaluation and Treatment of Tinnitus: A Comparative Effectiveness Review

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

I. Background and Objectives for the Systematic Review

Background

Prevalence

Tinnitus is the perception of sound in the absence of an external auditory stimulus. Tinnitus is a distressing condition that can disturb one's day-to-day life in a number of ways including 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]

Causes

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—ranging from impacted wax to acoustic tumors—that warrant medical attention. The prevalence of tinnitus increases with age and noise exposure.[2] 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. Military personnel are commonly exposed to high levels of noise and, indeed, tinnitus is the most common service-connected disability among U.S. veterans. [1] Traumatic brain injury (concussion) is a common cause of tinnitus in both veterans and nonveterans. 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).

Severity and Comorbidities

The severity of tinnitus experienced by patients may vary or depend on 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 visual information does not help them understand that their tinnitus is not an external sound. It is common for tinnitus to aggravate or be aggravated by mental health conditions.

Classification of Subtypes

In both clinical and academic contexts, there is no consensus in 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.[5] 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

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

temporomandibular joint (TMJ) origin.[6] 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.[6] Somatic tinnitus can be treated by identifying the source or the underlying condition and appropriately treating it.[6] 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.[7] Neurophysiologic tinnitus (more commonly known as subjective idiopathic tinnitus), in which the perceived sound originates from the auditory nervous system, is the most common diagnosis, since most patients experience this subjective form of tinnitus.[6] This form of tinnitus is nonpulsatile and most often bilateral (affects both ears). It can be heard only by the patient and cannot be directly observed by a physician, thus making it difficult to evaluate. These "phantom sounds" are attributed to a disruption in the neurological auditory pathway. 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.[8]

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.

Measures

Various measures can be used to evaluate the presence and severity of the tinnitus.[9] There are at least a dozen questionnaires for assessing the impact of tinnitus that have been validated. Psychological grading scales can aid in the discrimination between clinically significant and nonsignificant tinnitus.[10] If the patient reports constant or near-constant perception of tinnitus, the condition is identified as chronic tinnitus. 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.

Visual analog scales (VASs) are well known psychometric measures of subjective attitudes and characteristics. Most commonly, with a VAS scale, patients specify their level of agreement to a statement by indicating a position along a continuous line between two end points. The VAS can be used to assess loudness, pitch, and disturbance of the tinnitus.[11] Tinnitus questionnaires contain a series of questions, and patients select a response to each question from the given choices (usually a graded scale). For example, questionnaires such as the Tinnitus Handicap Inventory and the Tinnitus Reaction Questionnaire 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 effectiveness of tinnitus interventions.[12] Such effectiveness is referred to as "responsiveness," which emphasizes effect sizes, content validity, and response scaling that enables detection of change.[13,14] The Tinnitus Functional Index 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.[15]

Review Inclusions

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Given the diagnostic challenges presented by the multiple etiologies of tinnitus and the highly subjective presentation of its symptoms, reviewing the comparative effectiveness of the clinical measures used to identify patients for further evaluation or treatment will form the initial part of our review. The remainder of the review will focus on adult patients with subjective idiopathic (nonpulsatile) tinnitus. Adults diagnosed with unilateral and/or pulsatile tinnitus need to be evaluated for other medical conditions (such as acoustic neuromas). Our review will include only those cases in which a medically serious underlying pathology as the source of the tinnitus has already been ruled out. Furthermore, our review will not include those whose tinnitus is a side effect of a drug where the tinnitus can be eliminated by a change in medication. It will also exclude, in Key Questions (KQs) 2 and 3, cases of those who are seeking reassurance or information but who are not bothered by their tinnitus sufficiently to seek further treatment. In sum, our review will focus on adult patients with subjective idiopathic (nonpulsatile) tinnitus who form the majority of those seeking help because tinnitus interferes with some aspect of their lives to the extent that they seek treatment for it.

Tinnitus Treatments

Various clinical evaluation instruments, as identified above, can be used to characterize a subjective diagnosis and evaluate the severity of tinnitus. Some patients with tinnitus may receive "no treatment" following a medical examination 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 tinnitus-specific intervention is indicated, the patient can be treated by suggesting ways to cope with the discomfort associated with tinnitus, including sound therapy or relaxation or stress-reduction techniques. Treatment methods are not able to reduce or eliminate the sensation of tinnitus on any consistent basis. Therefore, treatment should focus on providing methods to reduce reactions to tinnitus. While drugs are used for tinnitus, there is no drug that has been approved specifically for its treatment. Behavioral methods should be used before considering the use of drugs. Drugs can be used to treat comorbid conditions such as anxiety and depression. The range of interventions therefore can include, but is not limited to, medical/surgical treatments, sound treatments/associated technologies, and psychological/behavioral treatments as outlined below.

Medical/surgical treatments

Pharmacological Treatment

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 (see Table 1 for examples).[16-20] These treatments have been indirect solutions because they focus on tinnitus-associated symptoms such as depression, stress, or sleep disturbance.[21] However, newer medications that attempt to

modulate the central hearing pathways, such as pramipexole are being investigated, and this may have promise for reducing the perception of tinnitus.[22]

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

Botox = botulinum toxin type A

Temporomandibular Joint Treatment

Tinnitus, vertigo, and otalgia are symptoms that have been linked to temporomandibular joint (TMJ) disease.[23] TMJ disease consists of a collection of medical and dental conditions that affect the temporomandibular joint, 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.[24] Treatment of TMJ disease 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.[25] While evidence is equivocal regarding the ability of treatment for TMJ disorders to reduce the effects of tinnitus, this approach may be helpful in some patients.

Transcranial Magnetic Stimulation

Electrical stimulation has been used to stimulate the auditory system and 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.[26] Transcranial magnetic stimulation (TMS), although not commonly used, delivers an electrical field to the cerebral cortices modulating the excitability in the area of the cerebral cortex believed to be associated with tinnitus.[27]

Complementary and Alternative Medicine Therapies

Complementary and alternative medicine therapies—including *Gingko biloba* extracts, acupuncture, and hyperbaric oxygen—are also being used by patients with tinnitus. Extracts from *G. 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 *G. biloba* plant.[28]

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.[29]

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

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.[30] 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 alternative 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.[31-34]

Sound treatments/technologies

Hearing Aids

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.[35]

Cochlear Implants

Cochlear implants may reduce tinnitus by masking newly perceived 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).[26]

Sound Generators

Tinnitus masking was developed in the 1970s. With masking, the purpose is not to cover up, or "mask," the patient's tinnitus. The purpose is to use sound to achieve a sense of relief from the stress or tension caused by tinnitus.[36] This is done by using ear-level sound generators, often called "maskers," that generate wideband noise. The word "masking" has created confusion—the method should be 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,[36] they are generally not covered under health insurance plans.[37]

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.[38] 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."[39] 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, meaning the patient does not normally pay attention to the tinnitus and does not react to it when it does come into consciousness.[38,39]

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.[40] 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."[41]

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, but those who are most distressed by tinnitus may be psychologically vulnerable.[42] Interventions such as cognitive behavioral therapy may effectively increase quality of life by increasing the patient's ability to deal with chronic tinnitus by restructuring thought patterns and habituating those patterns when the patient is reacting to tinnitus.[43] Cognitive behavioral therapy 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.[44]

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. 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.[45] Listening to the audio signal is thought to reduce the perceived ringing and muscle tension.

Educating patients about their tinnitus has been proposed to improve the management of tinnitus-related symptoms and their associated discomfort.[45] 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 potentially a lifetime of tinnitus management.[5]

Relaxation therapies also offer strategies to focus the patient's attention away from the sound, aiming to psychologically improve their symptoms.[46] 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 are an important component of cognitive behavioral therapy.

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 VA medical centers. PTM uses elements of hearing aids, masking, TRT, and cognitive behavioral therapy. 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.[35,47]

Justification for Review

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.[48] Recent research findings from cognitive and auditory neuroscience studies have advanced our 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. The comparative effectiveness review (CER) we propose offers an opportunity to explore prognostic factors and strategies for the optimal management of tinnitus.

The range of tinnitus treatments has prompted the need for a CER. 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.[49] The usability of the TRI flowchart is limited as it reflects a biomedical approach: an approach that would be used by medical physicians not by providers 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*[44] for the commissioning of tinnitus services and for managing tinnitus from primary care onwards.[50] Comparable guidelines are currently not standardized in the United States, although individual efforts and strategies appear in the research literature.[6,51]

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. Our proposed review aims to clarify the effectiveness of the various tinnitus treatments currently in use and their measurable outcomes.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

II. The Key Questions

Public Comments

The Key Questions (KQs) were posted for public comment on the Effective Health Care Program Web site between October 11 and November 10, 2011. Fifty-nine comments were received. When literature was cited or summarized, it was literature related to the current review. Most responses were attempts to answer the KQs based on the responders' professional experience in working with patients who have tinnitus. Public comments regarding the KQs did motivate the following changes to our KQs:

- KQ 1 has been amended to be inclusive of tinnitus evaluation scales beyond those specifically listed to clarify that the investigation is not restricted to the examples provided.
- To investigate the complex interaction between tinnitus and sleep disturbances, sleep modification is considered as an intervention therapy in KQ 2 and sleep patterns as a patient characteristic in KQs 2 and 3.
- Noise exposure as a patient characteristic has been subdivided by source (environmental, recreational, and work-related [including active or past military duty] and occupational hazards) in KQs 2 and 3 to allow for consideration of the unique features of exposure source.
- In response to public feedback, third-party coverage has been added as a patient characteristic in KQ 3.
- KQ 4 (What prognostic factors for patients with subjective idiopathic [nonpulsatile] tinnitus have been identified in the literature?) has been removed as a KQ because an earlier amendment added "Prognostic Factors" as a component of KQ 3.
- In response to two public comments asking, "What about unilateral tinnitus?," we have replaced all references to "neurophysiologic (bilateral, nonpulsatile) tinnitus" in the background document and in KQs 2 and 3 with "subjective idiopathic (nonpulsatile) tinnitus" (which could be bilateral or unilateral) and provided further clarification in the Background section that: "Adults diagnosed with unilateral and/or pulsatile tinnitus need to be evaluated for other medical conditions (such as acoustic neuromas). Our review will include only those cases in which a medically serious underlying pathology as the source of the tinnitus has already been ruled out." This has also been amended in the PICOTS framework under populations.

Key Question 1 and PICOTS

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)**

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Adult patients presenting with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds, etc.)

Note: "Adults" for *all* KQs will include individuals 18 years of age and older.

- **Interventions**

  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., Tinnitus Handicap Inventory, Tinnitus Reaction Questionnaire, Tinnitus Functional Index, Visual Analog Scale, and Tinnitus Severity Index, etc.])

- **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)

Key Question 2 and PICOTS

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)?

- **Population(s)**

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

Note: For KQs 2 and 3, adults diagnosed with unilateral and/or pulsatile tinnitus need to be evaluated for other medical conditions (such as acoustic neuromas). Our 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:

  - 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: *G. biloba* extracts; acupuncture; hyperbaric oxygen therapy; and diet, lifestyle, and sleep modifications (caffeine avoidance, exercise)

  - Sound Treatments/Technologies[1]

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

  - Psychological/Behavioral

    - Cognitive behavioral therapy
    - Biofeedback
    - Education
    - Relaxation therapies

[1] Information on the FDA-approval status of devices is included in Appendix A.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

    - Progressive Tinnitus Management

  - Combination therapies

    - Any combination of tinnitus interventions (e.g., pharmacological treatment with cognitive behavioral therapy)

- **Comparators**

  Placebo; no treatment; wait list; treatment as usual; other intervention/treatment

- **Outcomes**

  - Final outcomes:

    1. Sleep disturbance
    2. Discomfort
    3. Anxiety
    4. Depression
    5. Self-reported loudness
    6. Quality of life

  - Adverse effects
    1. Worsening of tinnitus
    2. Sedation
    3. Surgical complications

- **Timing or followup**

  No restrictions

- **Setting**

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

Key Question 3 and PICOTS

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

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

- **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 KQ 2.

- **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, mental health disorders, and duration of tinnitus
  - Patient characteristics: age, gender, 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, ototoxicity, tinnitus duration since onset, subcategory of tinnitus, severity of tinnitus

- **Outcomes**

  - Final outcomes:
    1. Time until improvement
    2. Sleep disturbance
    3. Discomfort
    4. Anxiety
    5. Depression
    6. Self-reported loudness
    7. Quality of life
    8. Return to "normal" work

  - Adverse effects
    1. Worsening of tinnitus
    2. Sedation
    3. Surgical complications

- **Timing or followup**

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

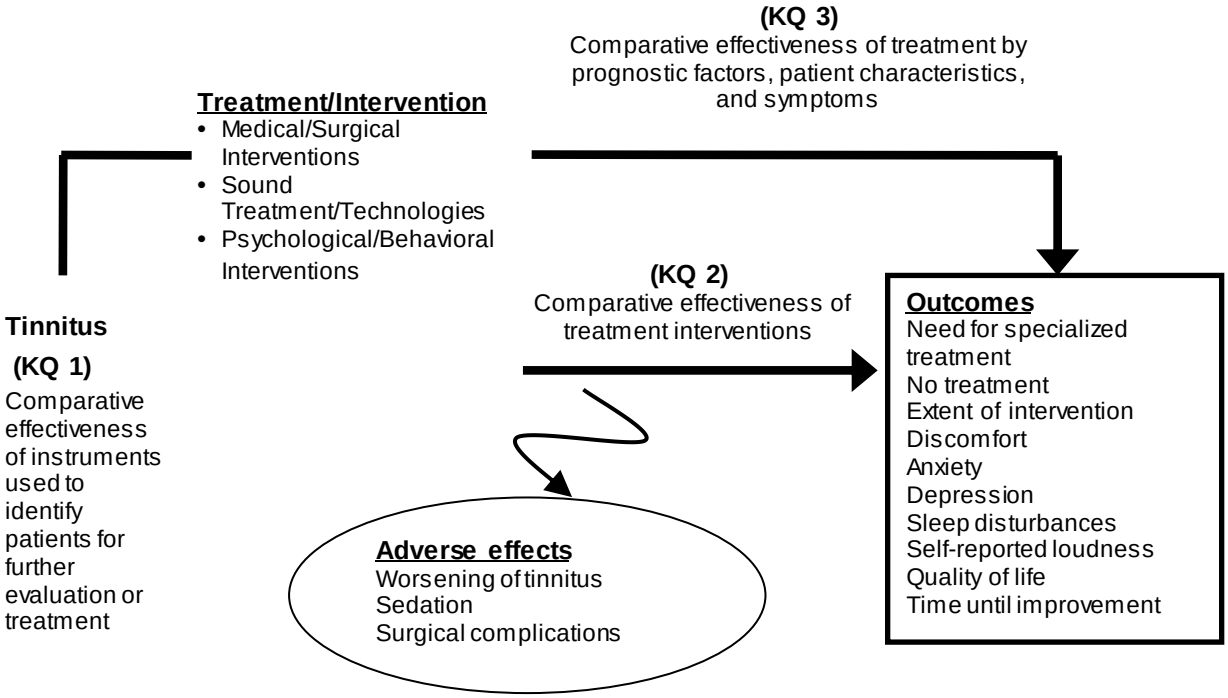
No restrictions

- **Setting**

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

III. Analytic Framework

Figure 1: Preliminary analytic framework for treatments of tinnitus



Abbreviations: KQ = key question

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria will be based on the eligibility criteria from the PICOTS listed above in section II. The search strategy will be limited to publications in our selected databases from 1970 onward. Based on input from our Technical Expert Panel (TEP), that the majority of available studies will be published in English-language journals, we will exclude non–English-language publications.[52,53]

We will include studies, provided they are randomized controlled trials (RCTs) or observational studies with true control groups (e.g., cohort, case control). Meta-analyses and systematic and narrative

reviews will be excluded, but reference lists will be evaluated for potentially relevant citations. Case reports, case series, editorials, comments, letters, opinion pieces, and abstracts will be excluded (see Table 2).

Citations meeting our search criteria (see section B) will be downloaded into Reference Manager® 12 (Thomson Reuters, New York, NY) and then imported into a systematic review software program, DistillerSR (2011, Ottawa, Canada), for screening. Once in DistillerSR, citations will be 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 will proceed to full-text rating. Full-text inclusion, data abstraction, and quality assessment will be completed by two team members at all times. All disagreements will be resolved through discussions with the synthesis team, and inclusion results will be reviewed by a third person.

Study authors will be contacted via e-mail for missing outcome or design data. Reference lists of all included papers will be screened for potentially relevant papers that have not already been screened. Grey literature will be searched; see the search strategy below in section B.

Table 2. Inclusion and Exclusion Criteria

Category	Inclusion Criteria	Exclusion Criteria
Population	• KQ 1: Adult (≥18 yrs) patients who visit primary care practitioners with symptoms of tinnitus (e.g., ringing in the ears, whooshing sounds, etc.) • KQs 2 & 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	• Patients under 18 years of age • Adults diagnosed with pulsatile tinnitus • Unilateral cases with specific medical diagnoses (e.g., pulsatile tinnitus with acoustic neuroma) • Tinnitus as a side effect of drugs • Nonhuman
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 abstracted from data in the papers • Controlled experimental studies (manipulation of treatment)	• Meta-analysis, systematic and narrative reviews (excluded but pulled for full reference list review), case reports/studies, and case series • Editorials, comments, letters, opinion pieces, and abstracts

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Other criteria	• Studies must address one or more of the following for tinnitus:
	  • Instruments used to identify patients for further evaluation or treatment (KQ 1)
	  • Treatment modality (KQ 2)
	  • Predictors of treatment outcomes (KQ 3) (prognostic factors, patient characteristics, and symptom characteristics)
	  • Treatment approaches for adults at risk for a tinnitus diagnosis (KQs 1,2,& 3)	

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Search Strategy

Tinnitus is well indexed in the medical bibliographic databases, and there are few alternative terms that need to be included in the search strategy.

The major challenge is that tinnitus appears to be a rapidly developing field, and there are a substantial number of studies that are either not yet completed or were recently completed but not yet published. This fact points to the importance of a comprehensive search of the grey literature for this topic.

The search strategy will use combinations of controlled vocabulary (medical subject headings [MeSH®], keywords) and text words. The search will be restricted to human-focused studies (specifically removing those results that only include animal data) and will be limited by date to research published from 1970 onward. Our search strategy is listed below.

1. Tinnitus/ or tinnitus.ti.
2. animals/ not humans/
3. 1 not 2
4. limit 3 to yr="1970 –Current"
5. limit 4 to English language

The search will be conducted in six databases: MEDLINE®, EMBASE®, Cochrane Central, PsycINFO®, AMED©, and CINAHL®. These databases have been 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. The search strategy will be peer reviewed by a second librarian at our center.

Review of reference lists of eligible studies at full-text screening will be undertaken. Reference lists of all systematic reviews and meta-analyses (which will be separately coded for retrieval during screening) will be reviewed. Any potentially relevant citations will be cross-checked within our citation database. Any references not found within the database will be retrieved and screened at full text.

Grey Literature Search

The search strategy for grey literature will closely resemble the terms used in the search of bibliographic databases. Terms for tinnitus will be searched with a focus on human studies. The aim of the grey literature search is to locate any information that has not yet reached more mainstream or indexed sources. As such, unpublished studies and ongoing studies are the focus of these searches.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Three types of grey literature sources will be searched: regulatory agency Web sites, clinical trial databases, and conference sources. The regulatory information includes the FDA, Health Canada, and the European Medicines Agency. The clinical trial databases that will be searched include: clinicaltrials.gov, clinicaltrialsregister.eu, metaRegister of Current Controlled Trials, Clinical Trial Registries, Clinical Study Results, and WHO Clinical Trials. Conference papers will be searched in the Conference Papers Index and Scopus for the last 2 years only. This is to allow for 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 will be 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 UK

The Scientific Resource Center will also request the Scientific Information Packages for drugs and devices.

Updating of the Search

At the time the draft peer review report is submitted, an update of our search in all specified databases (see above) will be undertaken.

Incorporation of Public and Peer Review Suggestions for Literature

Any publications suggested by peer reviewers or from public comment will be documented and verified within our citation database. Any references not included within our citation database will be retrieved and screened for eligibility at the stage of the full–text review.

C. Data Abstraction and Data Management

The Evidence-based Practice Center (EPC) staff members and clinical experts conducting this review will jointly develop the evidence table to be used to abstract data from the studies. The table will be 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 will include but not be limited to age, sex (percentage of females), racial composition, and comorbidities. When available, data will also be collected on psychoacoustic measures, sound level tolerance, abnormal

loudness growth, site where study participants were recruited, setting, and service provider. When applicable, data will also be collected on which discipline the research arose from. In addition to outcomes related to treatment effectiveness, all available data on harms or adverse effects of treatments will also be abstracted.

To ensure quality control, the team will abstract several articles into the evidence table and then reconvene as a group to discuss the utility of the table design. This process will be repeated until it is decided that the table includes the appropriate categories to gather the information contained in the articles. All team members will share the task of initially entering information into the evidence table. Another team member will review the articles and edit all initial table entries for accuracy, completeness, and consistency. The full research team will meet regularly during the article abstraction period to discuss any conflicts or issues related to the data abstraction process.

D. Assessment of Methodological Quality of Individual Studies

To assess individual study quality, we will use methods recommended by the Agency for Healthcare Research and Quality (AHRQ) for its EPC Program in Chapter 5 of its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).[54] Two raters will assess the quality of individual studies using standardized quality assessment tools. We will minimize inconsistency among raters by providing standardized instructions and clear decision rules. Disagreement between raters will be resolved by consensus.

Quality 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,[55] the Jadad scale[56] for RCTs, and Hayden et al.[57] for prognostic studies. Additional items were needed to describe the population for case-control studies (five items), cohort studies (2 items), and before-after studies (2 items). Each quality item will 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, we will graph the responses and discuss any problem areas. An overall quality score will not be calculated. See Appendix B for a copy of the quality assessment tools.

E. Data Synthesis

Qualitative Synthesis

Study results will be presented in three sections based on the three KQs. All included studies will be summarized in narrative form, and summary tables will be created showing key study characteristics (i.e., population characteristics, treatment interventions, study outcomes, sample sizes, settings, funding sources, and comparator treatments [type, duration, and provider]), methodological limitations, and any other important aspect related to each KQ. If clinical groups are too heterogeneous to permit meta-analysis, a separate qualitative analysis will be presented and graphical representation may be used to display main study outcomes.

Quantitative Synthesis

The decision to pool individual study results will be based on clinical judgment with regard to comparability of study populations, diagnostic standard, treatments, and outcome measures. If meta-analysis is warranted, we will utilize the generic inverse variance method in Review Manager v5.1.6 (Nordic Cochrane Centre, Copenhagen, Denmark) and the DerSimonian and Laird random- and fixed-effects models[58] to generate summary measures of effect (odds ratios) for each outcome. We will use Borenstein et al.'s formulae to convert data in other formats besides odds ratios (e.g., mean differences) into log odds ratios for input into Review Manager.[59] We will employ the I^2 test to assess statistical heterogeneity. Where homogeneity is present, we will report summary results with the fixed-effects model; otherwise we will use the random-effects model. Results will be considered significant at the 5 percent level. Subgroup (sensitivity) analysis will be undertaken to identify the sources of heterogeneity.

F. Grading the Evidence for Each Key Question

We will assess the overall strength of evidence for each KQ using the EPC method for intervention studies, which is based on methods developed by the GRADE Working Group.[54,60] Several domains of quality across studies may influence the overall strength of evidence for these KQs, including:

1. Risk of bias (how the study type and study design and conduct may have contributed to systematic error [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 spread of the summary effect size.
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.
4. 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)
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 will be classified into four grades based on the AHRQ EPC Program approach: high, moderate, low, or insufficient.[54,60]

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

G. Assessing Applicability

Applicability may be affected by differences between what occurs in research and what happens in everyday clinical practice. We will assess applicability in accordance with *Assessing Applicability When Comparing Medical Interventions: AHRQ and the Effective Health Care Program*.[61] The basis for applicability assessment of our findings will be 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.

V. References

1. American Tinnitus Association. ATA's Top 10 Most Frequently Asked Questions. Available at: http://www.ata.org/for-patients/faqs. Accessed February 21, 2012.
2. Davis A, El Rafaie A. Epidemiology of tinnitus. In: Tyler RS, ed. Epidemiology of tinnitus. San Diego,CA: Singular Publishing Group; 2000. p. 1-24.
3. American Tinnitus Association. Press Release: August 24, 2011. Two ATA Scientific Advisory Committee Members Receive Department of Defense Grant...Will Study Blast- and Concussion-Induced Tinnitus. Available at: http://www.ata.org/about-ata/news-pubs/press-releases#DoDGrant. Accessed February 21, 2012.
4. Savage J, Cook S, Wadell A. Tinnitus. Clin Evid (Online) 2007 Aug 1;2007. pii: 0506. PMID: 19454115.
5. Henry JA. Key informant interview. 2011 Jul 26.
6. Henry JA, Zaugg TL, Myers PJ, et al. A triage guide for tinnitus. J Fam Pract 2010 Jul;59(7):389-93. PMID: 20625568.
7. British Tinnitus Association.Tinnitus: Ten Top Tinnitus Tips for GPs. Available at: http://www.tinnitus.org.uk/pages/337. Accessed February 21, 2012.
8. Holgers K-M. Mechanisms and classification of tinnitus: a discussion paper. Audiol Med 2003;1(4):238-41.
9. 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 Oct;26(5):388-93. PMID: 11678946.
10. Erlandsson S. Psychological profiles of tinnitus in patients. In: Tyler RS, ed. Tinnitus handbook. San Diego, CA: Singular Publishing Group; 2000. p. 25-58.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

11. Figueiredo RR, Azevedo AA, Oliveira PM. Correlation analysis of the visual-analogue scale and the Tinnitus Handicap Inventory in tinnitus patients. Revista Brasileira de Otorrinolaringologia 2009Jan-Feb;75(1):76-9. PMID: 19488564.
12. 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 Aug;143(2):181-5. PMID: 20647116.
13. Lipsey MW. Design sensitivity: statistical power for experimental research. Newburry Park, CA: Sage Publications, Inc.; 1990.
14. Kazdin AE. Research design in clinical psychology. 4th ed. Needham Heights, MA: Allyn & Bacon; 2003.
15. Meikle MB, Henry JA, Griest SE, et al. The Tinnitus Functional Index: development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear 2011 Dec 12 [Epub ahead of print]. PMID: 22156949.
16. Baldo P, Doree C, Lazzarini R, et al. Antidepressants for patients with tinnitus. Cochrane Database Syst Rev 2006 Oct 18;(4):CD003853. PMID: 17054188.
17. Johnson RM, Brummett R, Schleuning A. Use of alprazolam for relief of tinnitus. A double-blind study. Arch Otolaryngol Head Neck Surg 1993 Aug;119(8):842-5. PMID: 8343245.
18. Jalali MM, Kousha A, Naghavi SE, et al. The effects of alprazolam on tinnitus: a cross-over randomized clinical trial. Med Sci Mon 2009 Nov;15(11):PI55-60. PMID: 19865063.
19. Kalcioglu MT, Bayindir T, Erdem T, et al. Objective evaluation of the effects of intravenous lidocaine on tinnitus. Hear Res 2005 Jan;199(1-2):81-8. PMID: 15574302.
20. Agarwal L, Pothier DD. Vasodilators and vasoactive substances for idiopathic sudden sensorineural hearing loss. Cochrane Database Syst Rev 2009 Oct 7;(4):CD003422. PMID: 19821308.
21. Noble W. Treatments for tinnitus. Trends Amplif 2008 Sep;12(3):236-41. PMID: 18635586.
22. Sziklai I, Szilvassy J, Szilvassy Z. Tinnitus control by dopamine agonist pramipexole in presbycusis patients: a randomized, placebo-controlled, double-blind study. Laryngoscope 2011 Apr;121(4):888-93. PMID: 21433025.
23. Tuz HH, Onder EM, Kisnisci RS. Prevalence of otologic complaints in patients with temporomandibular disorder. Am J Orthod Dentofacial Orthop 2003 Jun;123(6):620-3. PMID: 12806339.
24. Wright EF, Syms CA III, Bifano SL. Tinnitus, dizziness, and nonotologic otalgia improvement through temporomandibular disorder therapy. Milit Med 2000 Oct;165(10):733-6. PMID: 11050868.
25. 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 Jan-Feb;4(1):51-7. PMID: 2012671.
26. Henry JA, Dennis KC, Schechter MA. General review of tinnitus: prevalence, mechanisms, effects, and management. J Speech Lang Hear Res 2005 Oct;48(5):1204-35. PMID: 16411806.
27. Langguth B, Hajak G, Kleinjung T, et al. Repetitive transcranial magnetic stimulation and chronic tinnitus. Acta Otolaryngol Suppl 2006 Dec;(556):102-5. PMID: 17114153.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

28. Hilton M, Stuart E. Ginkgo biloba for tinnitus. Cochrane Database Syst Rev 2004;(2):CD003852. PMID: 15106224.
29. Park J, White AR, Ernst E. Efficacy of acupuncture as a treatment for tinnitus: a systematic review. Arch Otolaryngol Head Neck Surg 2000 Apr;126(4):489-92. PMID: 10772302.
30. 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 Oct;119(10):791-8. PMID: 16259656.
31. Curing Tinnitus Permanently. Curing Tinnitus at Home with Natural Methods. Available at: http://curingtinnituspermanently.com/. Accessed February 21, 2012.
32. Keate B. Diet and tinnitus: what to eat . . . and what not to eat. Available at: http://www.tinnitusformula.com/infocenter/articles/treatments/diet.aspx. Accessed February 21, 2012.
33. Tinnitus and your diet. New Tinnitus Treatments Blog. Available at: http://www.tinnitustreatments.org/tinnitus-and-your-diet.html. Accessed February 21, 2012.
34. Tinnitus Remedies Web Site. Tinnitus Relief Through Diet—Foods to Avoid to Relieve Tinnitus. Available to: http://www.thetinnitussite.info/tinnitus-relief-2/tinnitus-relief-through-diet-foods-to-avoid-to-relieve-tinnitus. Accessed February 21, 2012.
35. Henry JA, Zaugg TL, Myers PJ, et al. Progressive audiologic tinnitus management. ASHA Leader 2008;13(8):14-7.
36. Hobson J, Chisholm E, El Refaie A. Sound therapy (masking) in the management of tinnitus in adults. Cochrane Database Syst Rev 2010 Dec 8;12:CD006371. PMID: 21154366.
37. Cigna. Cigna medical coverage policy. Tinnitus treatment services and devices. Available at: http://www.cigna.com/assets/docs/health-care-professionals/coverage_positions/mm_0220_coveragepositioncriteria_tinnitus_instr_devices_retraining_ther.pdf. Accessed February 21, 2012.
38. Phillips JS, McFerran D. Tinnitus Retraining Therapy (TRT) for tinnitus. Cochrane Database Syst Rev 2010 Mar 17;(3):CD007330. PMID: 20238353.
39. Jastreboff PJ, Hazell JW. A neurophysiological approach to tinnitus: clinical implications. Br J Audiol 1993 Feb;27(1):7-17. PMID: 8339063.
40. 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 Jun;87(6):330-9. PMID: 18561116.
41. Davis PB, Paki B, Hanley PJ. Neuromonics Tinnitus Treatment: third clinical trial. Ear Hear 2007 Apr;28(2):242-59. PMID: 17496674.
42. Langguth B, Kleinjung T, Landgrebe M. Tinnitus: the complexity of standardization. Eval Health Prof 2011 Dec;34(4):429-33. PMID: 21224265.
43. Martinez-Devesa P, Perera R, Theodoulou M, et al. Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev 2010 Sep 8;(9):CD005233. PMID: 20824844.
44. Department of Health. Provision of services for adults with tinnitus: a good practice guide. London: Central Office of Information; 2009.
45. Dobie RA. A review of randomized clinical trials in tinnitus. Laryngoscope 1999 Aug;109(8):1202-11. PMID: 10443820.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

46. 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.
47. Henry JA, Zaugg TL, Myers PJ, et al. The role of audiologic evaluation in progressive audiologic tinnitus management. Trends Amplif 2008 Sep;12(3):170-87. PMID: 18628281.
48. 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 Oct;11(42):1-294. PMID: 17927921.
49. Searchfield G. A commentary on the complexity of tinnitus management: clinical guidelines provide a path through the fog. Eval Health Prof 2011 Dec;34(4):421-8. PMID: 21224266.
50. 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 Nov 19 [Epub ahead of print]. PMID: 21087449.
51. Henry JA, Schechter MA, Loovis CL, et al. Clinical management of tinnitus using a "progressive intervention" approach. J Rehabil Res Dev 2005 Jul-Aug;42(4 Suppl 2):95-116. PMID: 16470467.
52. 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 Feb;31(1):115-23. PMID: 11914306.
53. 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 Sep;53(9):964-72. PMID: 11004423.
54. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; August 2011. AHRQ Publication No. 10(11)-EHC063-EF. Chapters available at: www.effectivehealthcare.ahrq.gov.
55. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOW) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed February 21, 2012.
56. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996 Feb;17(1):1-12. PMID: 8721797.
57. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006 Mar 21;144(6):427-37. PMID: 16549855.
58. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986 Sep;7(3):177-88. PMID: 3802833.
59. Borenstein M, Hedges LV, Higgins JP, et al. Introduction to meta-analysis. Chichester, United Kingdom: John Wiley & Sons Ltd; 2009.
60. 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 May;63(5):513-23. PMID: 19595577.
61. 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 Nov;64(11):1198-207.

VI. Definition of Terms

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

No additional definitions to those provided in the text above.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness Reviews (CERs), the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC Program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures:

Please identify team members by their role, and not by name. Disclosures are those that one would include in submitting a manuscript.

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

XIII. Role of the Funder

This project was funded under Contract No. HHSA 290-2007-10060-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A:

Type of Drug	Drug Name (where applicable)	Comments
Amitriptyline	Elavil, Tryptizol, Laroxyl, Sarotex, Lentizol	Elavil FDA ApprovalAmitriptyline Hydrochloride FDA Approval Amitriptyline Hydrochloride FDA Approval
Notriptyline	Sensoval, Aventyl, Pamelor, Norpress, Allegron, Noritren and Nortrilen	Aventyl FDA Approval Pamelor FDA Approval
Trimipramine	Surmontil, Rhotrimine, Stangyl	Surmontil FDA Approval
Fluoxetine	Prozac, Sarafem, Fontex	Prozak FDA Approval Sarafem FDA Approval
Paroxetine	Aropax, Paxil, Seroxat, Sereupin	Paxil FDA Approval Paroxetine FDA Approval
	Alprazolam	FDA Approval
Trazodone	Desyrel, Oleptro, Beneficat, Deprax, Desirel, Molipaxin, Thombran, Trazorel, Trialodine, Trittico, and Mesyrel	Desyrel FDA Approval Oleptro FDA Approval Trialodine FDA Approval Trazodone FDA Approval
Pramipexole	Mirapex, Mirapexin, Sifrol	Mirapex FDA Approval Pramipexole FDA Approval
Prostaglandin E1	Alprostadil	Alprostadil FDA Approval
Nicotinic acid		
Intravenous lidocaine		Lidocaine FDA Approval
Naftidrofuryl	Nafronyl or as the oxalate salt naftidrofuryl oxalate or nafronyl oxalate	
Gabapentin	Fanatrex, Gabarone, Gralise, Neurontin, Nupentin	Gabapentin FDA Approval

Type of Device	Comments		
	Company	**Device**	**510(k) Number**
Cochlear Implants	KARL STORZ ENDOSCOPY-AMERICA, INC.	KARL STORZ MICRO-INSTRUMENT FOR COCHLEAR IMPLANTATION	K946332
	COCHLEAR AMERICAS	BIA300 SERIES IMPLANT AND ABUTMENT, BI300 IMPLANT, BA300 ABUTMENT Many others with PMA Approval	K100360

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

	COCHLEAR CORPORATION	Nucleus 24 Cochlear Implant System	**PMA Approved: P970051**
		Nucleus 22 Channel Cochlear Implant System	**PMA Approved: P840024/S071**
		Nucleus 22 Channel Cochlear Implant System for Adults and Children	**PMA Approved: P840024/S072**
		Nucleus 22 Channel Cochlear Implant System	**PMA Approved: P890027/S040**
		Nucleus 22 Channel Cochlear Implant System for Adults and Children	**PMA Approved: P890027/S041**
	MEDEL	MED-EL COMBI 40+ Cochlear Implant System with C40+, C40+S, and C40+GB Implants, CIS-PRO+ and TEMPO+ speech processors	PMA Approval: P000025
	ADVANCED BIONICS CORPORATION	Many with PMA Approval.	
	NEUROLEC		No Approval Found
Masking Devices	ASSOCIATED HEARING INSTRUMENTS	MICRO MASKER	K924991
	AUDIOTRONE	T-570 TINNITUS MASKER	K800701
		TA-641 TINNITUS INSTRUMENT	K800702
	BELTONE ELECTRONICS CORP.	MINUET MASKER; JUBILEE MASKER	K800784
	FOUNDATION FOR FLUENCY, INC	EDINBURGH MASKER	K800445
	GN RESOUND A/S	TINNITUS SOUND GENERATOR MODULE	K110932
		TINNITUS SOUND GENERATOR MODULE	K073636
	HAL-HEN CO., INC	NUVOX BEDSIDE TINNITUS MASKER	K802750
	HEARING INNOVATIONS, INC.	HISONIC-TRD TINNITUS RELIEF DEVICE	K013253
	MAGNATONE HEARING AID CORP. DBA PERSONA MEDICA	EVOK 900 SERIES HEARING AID/TINNITUS MASKER OPTION	K093715
	MARPAC, INC.	MODEL#1550 MARSONA(R) TINNITUS MASKER	K940567
		BEDSIDE TINNITUS MASKER #1500	K802234
	MICROBIO-MEDICS, INC.	321Q MINIMUM ENERGY TINNITUS SUPPRESSOR	K922572
	NEUROMONICS PTY LTD	NEUROMONICS TINNITUS TREATMENT	K043274

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

	PETROFF AUDIO TECHNOLOGIES	DIGITAL TINNITUS MASKING SYSTEM	K974501
	SIEMENS HEARING INSTRUMENTS, INC.	CUSTOM TCI (TINNITUS CONTROL INSTRUMENT)	K011364
		TCI (TINNITUS CONTROL INSTRUMENT	K003559
		TCI COMBI (TINNITUS CONTROL INSTRUMENT COMBINATION)	K003558
		CUSTOM TCI-COMBI (TINNITUS CONTROL INSTRUMENT COMBINATION	K011366
	STARKEY LABORATORIES, INC.	STARKEY TM-3, TM-5 HIGH FREQUENCY TINNITUS MASKER	K964216
		STARKEY TM AIR CONDUCTION TINNITUS MASKER	K963838
		STARKEY MA-3 AIR CONDUCTION COMBINATION HEARING AID/TINNITUS MASKER	K963995
		MODEL TM2-BEHIND-THE-EAR TINNITUS	K792214
		MODEL TM5 BEHIND EAR TINNITUS MASKER	K791790
		MODEL MA3 BEHIND-THE-EAR MASKER/HEARING	K791071
		TINNITUS MASKER	K781798
		TINNITUS RESEARCH AUDIOMETER	K802560
		CRESCENT TINNITUS RETAINING SOUND GENERATOR	K030180
	TELEX COMMUNICATIONS, INC.	TELEX TINNITUS-COMPANION	K984243
	TINNITUS CONTROL, INC.	TINNITUS PHASE-OUT	K061111
		TINNITUS RX	K031624
	TINNITUS TREATMENT CENTERS, INC	PILLOW MASKER, C2007M, C2008M,CE2000, WONDER EAR, MINI WONDER EAR, PT-2SM, PT-3SM, PT-3LFM, PT-3HFM	K982432
	VICAN INSTRUMENT CO.	TINNITUS MASKERS MODEL S584	K790190
	VICON INSTRUMENT CO.	TINNITUS MASKERS, MODELS S564&S574	K771769
		TINNITUS AID, MODEL S244	K770938
		TINNITUS DEVICES	K790064
Hearing Aids	A variety of companies produce this device.	Many available, not specific to tinnitus	Many FDA Approvals Exist
Acupuncture	A variety of companies produce this device.	Many available, not specific to tinnitus	Many FDA Approvals Exist
Transcranial Magnetic	NEUROSTAR TMS THERAPY SYSTEM, MODEL 1.1	NEURONETICS	K083538

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Stimulation	NEUROSTAR TMS SYSTEM		K061053

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Appendix B:

Quality Assessment Form: Jadad Scale: Randomized Control Trial

1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?	**Y / N**
2. Was the study described as double blind?	**Y / N**
3. Was there a description of withdrawals and dropouts?	**Y / N**

Scoring the items:

Either give a score of 1 point for each "Yes" or 0 points for each "No." There are no in-between marks.

Give 1 additional point if:	For question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated).
And / or:	If for question 2, the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).
Deduct 1 point if.	For question 1, the method to generate the sequence of randomization was described and it was inappropriate(patients were allocated alternatively, or according to date of birth, hospital number, etc.).
and / or:	If for question 2, the study was described as double blind but the method of double blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy).

Jadad Score _____

Guidelines for Assessment:

1. Randomization

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double blinding

A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawals in each group must be stated. If there were no withdrawals, it should be stated in the articles. If there is no statement on withdrawals, this item must be given no points.

Methods

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Centres: ☐- Single Centre
☐- Multi-Centre, national
☐-Multi-Centre, international

Design Features:

	Yes	No	Not Stated
Blinding			
• Participant blinded	☐	☐	☐
• Observer blinded	☐	☐	☐
• Care Provider blinded	☐	☐	☐
• Outcome Assessor blinded	☐	☐	☐

	Yes	No	Unclear
Was the allocation adequately concealed? E.g pharmacy controlled randomization scheme, sequentially numbered opaque, sealed envelope, sequentially numbered / coded identical containers, central randomization by phone	☐	☐	☐
Was the analysis based on intention to treat principle?	☐	☐	☐
Was the sample size justified?	☐	☐	☐
Were the statistical analysis methods described and appropriate?	☐	☐	☐
Was the outliers reported and appropriately dealt with in the analysis	☐	☐	☐

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation*****
   b) yes, eg record linkage or based on self-reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases *****
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls*****
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint)*****
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) *****
   b) study controls for any additional factor ***** (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) *****
   b) structured interview where blind to case/control status *****
   c) interview not blinded to case/control status
   d) written self-report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes *****
   b) no

3) Non-Response rate
   a) same rate for both groups *****
   b) non respondents described
   c) rate different and no designation

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

4) Were potential confounders measured and adequately addressed in the analysis? Yes☐ No ☐ Unclear ☐

5) Was the statistical analysis described? Yes☐ No☐ Unclear☐

6) Were missing data reported? Yes☐ No☐ Unclear☐

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community *****

b) somewhat representative of the average _____ in the community *****

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort*****

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) *****

b) structured interview *****

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes *****

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) *****

b) study controls for any additional factor ***** (This criteria could be modified to indicate specific control for a second

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

important factor.)

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

1) Assessment of outcome

a) independent blind assessment *****

b) record linkage *****

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) *****

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for *****

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *****

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

4) Were potential confounders measured and adequately addressed in the analysis? Yes ☐ No ☐ Unclear ☐

5) Was the statistical analysis described? Yes☐ No☐ Unclear☐

6) Were missing data reported? Yes☐ No☐ Unclear☐

Source: www.effectivehealthcare.ahrq.gov
Published Online: February 22, 2012

Quality Assessment for Prognosis Studies: Hayden criteria

	Yes	Partly	No	Unsure
1. Study Participation				
- The population of interest is adequately described for key characteristics.	☐	☐	☐	☐
- The sampling frame and method of recruitment are adequately described.	☐	☐	☐	☐
- Inclusion and exclusion criteria are adequately described.	☐	☐	☐	☐
2. Study Attrition				
- The proportion of sample completing the study and providing outcome data is adequate.	☐	☐	☐	☐
- Attempts to collect information on participants who dropped out are described.	☐	☐	☐	☐
- Reason for loss of follow- up are provided and adequately described for key characteristics	☐	☐	☐	☐
- No important differences in participants who completed the study and those who did not.	☐	☐	☐	☐
3. Prognostic factors				
- A clear description of a prognostic factors measured is provided.	☐	☐	☐	☐
- The prognostic factor measure and method are adequately valid and reliable to limit misclassification bias.	☐	☐	☐	☐
- Adequate study sample has complete data for prognostic factors.	☐	☐	☐	☐
- The method and setting are the same for all study participants.	☐	☐	☐	☐
- Appropriate methods are used if imputation is used for missing prognostic factor	☐	☐	☐	☐
4. Outcome measurement				
- A clear definition of outcome measurement is provided including duration of follow-up.	☐	☐	☐	☐
- The outcome measure and method are adequately valid and reliable to limit misclassification bias.	☐	☐	☐	☐
- The method and setting of measurement are the same for all study participants.	☐	☐	☐	☐
5. Confounding measurement				
- All important confounders are described and measured.	☐	☐	☐	☐
- Measurement for all confounders is adequately valid and reliable	☐	☐	☐	☐
- Important potential confounders are adjusted for in the study design.	☐	☐	☐	☐
- Important potential confounders are adjusted for in the analysis.	☐	☐	☐	☐
6. Analysis				
- The statistical analysis is appropriate for the design of the study.	☐	☐	☐	☐
- The strategy for model building is appropriate and is based on a conceptual framework	☐	☐	☐	☐
- The selected model is adequate for the design of the study.	☐	☐	☐	☐
- There is no selective reporting of results	☐	☐	☐	☐

Quality Assessment Form: Cross-Sectional Design

	Yes	No	Unclear
Study Population			
1. Did the authors clearly describe the population from which the participants were drawn?	☐	☐	☐
2. Were the inclusion and/or exclusion criteria described (no specific criteria)?	☐	☐	☐
3. Were the participants in the study representative of the population from which they were recruited?	☐	☐	☐
Outcome Measurements			
4. Was the outcome defined clearly (i.e., was the measure described in sufficient detail to be replicated)?	☐	☐	☐
5. Were those measuring the main outcome unaware of the exposure status?	☐	☐	☐
Exposure Measurements			
6. Was the exposure defined clearly (i.e., was the test method described in sufficient detail to permit replication)?	☐	☐	☐
7. Were those measuring the exposure unaware of outcome status?	☐	☐	☐
Statistical analysis			
8. Were potential confounders measured and adequately addressed in the analysis?	☐	☐	☐
9. Was the statistical analysis described?	☐	☐	☐
10. Were missing data reported?	☐	☐	☐