



## Clinical Policy Bulletin: Tinnitus Treatments

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(Replaces CPB 478)

### Policy

- I. Aetna considers transcutaneous electrical nerve stimulation (TENS) medically necessary durable medical equipment (DME) for members with severe tinnitus when all of the following criteria are met:
  - A. Medically correctable causes of tinnitus have been ruled out, *and*
  - B. Member has experienced severe tinnitus for more than 6 months, *and*
  - C. Member has tried and failed conservative tinnitus treatments, including counseling and reassurance, dietary modifications, and drug therapy.

Note: More than 10 TENS sessions per year are not considered medically necessary for the treatment of tinnitus because of a lack of evidence that more frequent TENS treatments provides additional clinically significant benefits for this condition.

- II. Aetna considers tinnitus instruments (e.g., maskers, hearing aids, or combination of maskers and hearing aids) experimental and investigational for the management of members with tinnitus because the effectiveness of these instruments has not been demonstrated in randomized controlled studies with large sample size and long-term follow-up evaluation.

Note: Tinnitus instruments such as maskers and hearing aids are approved by the Food and Drug Administration (FDA) and are classified as Class III devices; however, tinnitus masking is not approved for coverage by the Centers for Medicare & Medicaid Services (CMS).

- III. Aetna considers the following interventions experimental and investigational for the management of members with tinnitus (not an all-inclusive list):
  - Auditory perceptual training
  - Cochlear implants
  - Deep brain stimulation
  - Ear canal magnets
  - Electromagnetic stimulation
  - Hyperbaric oxygen therapy
  - Intra-tympanic administration of corticosteroids
  - Intravenous lidocaine

- Intravenous mexiletine
- Melatonin (alone or in combination with sulodexide)
- Neuromonics Tinnitus Treatment/Neuromonics Oasis device
- Noise/sound generators
- Repetitive transcranial magnetic stimulation (including continuous theta burst stimulation)
- Sequential phase shift sound cancellation treatment
- Tinnitus retraining therapy
- Transcranial electrical neuromodulation (e.g., alternating current stimulation, direct current stimulation, and random noise stimulation)
- Transmeatal laser irradiation (low-level laser)
- Vagus nerve stimulation

See also CPB 0132 - Biofeedback; CPB 0135 - Acupuncture; CPB 0172 - Hyperbaric Oxygen Therapy (HBOT); CPB 0238 - Chronic Vertigo; CPB 0469 - Transcranial Magnetic Stimulation and Cranial Electrical Stimulation; and CPB 0514 - Meniere's Disease Surgery.

## Background

Tinnitus is defined as the aberrant perception of noise or sound without any external stimulation. It may be unilateral or bilateral and has equal prevalence in women and men and is most prevalent between the ages of 40 and 70. Occasionally, tinnitus can also occur in children. Periodic bouts of mild, high-pitched tinnitus lasting for several minutes are common in normal-hearing individuals. Severe and persistent tinnitus can interfere with sleep and the ability to concentrate, causing great psychological distress. In extreme cases, patients with severe chronic tinnitus may consider suicide. Tinnitus can be classified into 2 types: (i) subjective tinnitus, and (ii) objective tinnitus.

Subjective tinnitus, which is more common, is audible only to the patient. It may arise from some types of electrophysiological disturbance anywhere in the auditory system -- the external ear canal, tympanic membrane, ossicles, cochlea, auditory nerve, brainstem or cerebral cortex. The underlying causes of subjective tinnitus include otological (presbycusis, noise-induced hearing loss, Meniere's disease, or chronic otitis media), metabolic (diabetes, thyroid diseases, hyperlipidemia, or zinc deficiency/vitamin deficiency), pharmacological (aspirin compounds, non-steroidal anti-inflammatory drugs, caffeine, nicotine, aminoglycosides, or antidepressants), neurological (whiplash, skull fracture/closed head trauma, multiple sclerosis, or following meningitis), psychological (depression or anxiety), as well as infectious and neoplastic (syphilis, acoustic neuroma, autoimmune diseases, or acquired immune deficiency syndrome) disorders.

Objective tinnitus, the less common type of tinnitus, usually refers to noises that can be heard by an examiner. The physician must put his/her ear against the patient's ear or use a stethoscope against the patient's external auditory canal. Objective tinnitus usually has a vascular (arteriovenous malformations/shunts, arterial bruits, hypertension, arteriosclerosis, venous hums, or aneurysms) or mechanical (Eustachian tube dysfunction, temporomandibular joint disease, palatal myoclonus, or idiopathic stapedal muscle spasm) origin (Schuler and Schleuring, 1994; Seidman and Jacobson, 1996).

The management of patients with tinnitus often depends on the severity of the condition. If the patient's activities of daily living are not affected by tinnitus, treatment options include counseling, reassurance, and/or behavioral and dietary modifications (avoidance of excessive noise, nicotine, salt, and caffeine). All medications should also be evaluated to eliminate ototoxic drugs. Currently, the medications for patients with severe tinnitus include amitriptyline (Elavil), alprazolam (Xanax), diazepam (Valium), and clonazepam (Klonopin);

however, none of these drugs has been approved by the Food and Drug Administration for the specific treatment of tinnitus.

#### Electrical Stimulation:

Another therapeutic modality is electrical stimulation (ES). In a review on tinnitus, Siedman and Jacobson (1996) indicated that ES is a possible treatment modality for patients with severe tinnitus. Hatton et al (1960) reported that only anodal (positive electrode) stimulation produced the suppressive effect. In general, ES is provided through electrodes in the vicinity of the ear. The exact mechanism(s) by which ES suppresses/reduces tinnitus is unclear. However, it has been postulated that positive electrical currents produce a hyperpolarization of nerve fibers, which inhibit and reduce spontaneous discharge rates (Portmann et al, 1983).

Hatton et al (1960) observed that the intensity of tinnitus was reduced in 15 (45.5 %) of 33 patients with ES. Chouard et al (1981) reported that 30 (47 %) of 64 patients achieved success (as determined by reduced intensity that lasted for a few days to more than 1 week) following electrotherapy. None of the 12 patients who received placebo stimulation attained relief. The authors stated that if a patient failed to achieve improvement after 2 to 3 sessions, it is unlikely that this form of therapy will be successful.

Engelberg and Bauer (1985) performed two experiments to examine the effects of transcutaneous electrical stimulation (TENS) on tinnitus. Experiment 1 had 10 subjects (18 ears) and improvement (defined as either a complete remission or a decrease in the frequency of tinnitus) was seen in 6 of them with tinnitus being eliminated in 3 ears. Experiment 2 employed a single-blind study design with 20 patients (experimental group, n = 10, 17 ears; control group, n = 10, 15 ears). It was found that 9 of 10 patients with 15 (88.2 %) of 17 ears reported improvement following stimulation. These changes lasted from 20 minutes to at least 6 months. On the other hand, only 1 patient (1 ear) in the control group improved (a 13 % decrease in frequency of tinnitus).

Steenerson and Cronin (1996) reported their findings of 246 patients with severe tinnitus of various etiologies treated with ES (a total of 6 to 10 sessions). One hundred and thirty patients (53 %) reported significant benefit (an improvement of at least 2 points in a 1 to 10 subjective rating scale) with 32 patients (13 %) having complete suppression of their tinnitus. At 3-month follow-up, 72 % had continuous benefit.

In a subsequent report, Steenereson and Cronin (1999) reported their findings in 500 patients with tinnitus who were treated with probe electrical stimulation. The authors reported that 53 % of patients showed decreases in their tinnitus as measured by a subjective rating scale. At 3-month follow-up, 72 % had no loss of benefit.

Rahko and Kotti (1997) treated 26 patients with transcutaneous nervous stimulation (TNS) for tinnitus. Except for 3 normal hearing patients, all had cochlear hearing losses. The authors found that tinnitus disappeared in none of the patients, but diminished in 7 patients, versus diminution of tinnitus in 3 in 24 nontreated controls.

In a study that evaluated the effects of psychological factors on the outcome of TENS for patients with chronic tinnitus (n = 27), Collet and associates (1987) found that the 15 patients (55.6 %) who did not improve showed higher pre-treatment scores of depression, psychasthenia, and schizophrenia. These findings indicated that patients having psychiatric problems such as those mentioned above are unlikely to benefit from treatment.

According to available literature, transcutaneous electrical stimulation for tinnitus is contraindicated in persons with the following conditions:

Persons taking medications for other diseases/conditions known to have a side effect of tinnitus, such as aspirin, Vasotec (enalapril maleate), etc.; or  
Persons with active ear disease; or  
Persons with cardiac pacemakers, implanted stapes prostheses or other implanted devices, which may be affected by electrical signals; or  
Persons with psychiatric problems such as schizophrenia, depression, hysteria, or hypochondria; or  
Women who are pregnant.

#### Masking Instruments:

Tinnitus masking instruments such as maskers, hearing aids, and tinnitus devices (combination of hearing aid and tinnitus masker) have been used for alleviating symptoms associated with tinnitus. However, the effectiveness of these instruments for treating tinnitus has not been established. These devices are all worn behind, or in either the same or opposite ear affected by tinnitus. Tinnitus maskers generate a grossly broad-band high-energy noise, which most patients find an excessive noise intrusion that is unacceptable and intolerable.

A review of 69 randomized clinical trials of therapies for tinnitus (Dobie, 1999) concluded that no treatment (pharmacotherapy, psychotherapy, and various non-drug treatments including masking) could yet be considered established in terms of providing reproducible long-term benefits, in excess of placebo effects.

A systematic review of the evidence for tinnitus treatments by *BMJ Clinical Evidence* concluded that tinnitus masking devices and hearing aids are of "unknown effectiveness" (Savage et al, 2011).

The Centers for Medicare and Medicaid Services (CMS, 2006) has concluded: "Tinnitus masking is considered an experimental therapy at this time because of a lack of controlled clinical trials demonstrating effectiveness and the unstudied possibility of serious toxicity in the form of noise induced hearing loss."

In a Cochrane review, Hobson et al (2010) examined the effects of sound therapy (masking) in the management of tinnitus in adults. Prospective, randomized controlled trials recruiting adults with persistent, distressing, subjective tinnitus of any etiology in which the management strategy included maskers, noise-generating device and/or hearing aids, used either as the sole management tool or in combination with other strategies, including counselling were included in this review. A total of 6 trials (553 subjects) were included in this review. Studies were varied in design, with significant heterogeneity in the evaluation of subjective tinnitus perception, with different scores, scales, tests and questionnaires as well as variance in the outcome measures used to assess the improvement in tinnitus sensation/quality of life. This precluded meta-analysis of the data. There was no long-term follow-up. These researchers assessed the risk of bias as medium in 3 and high in 3 studies. No side effects or significant morbidity were reported from the use of sound-creating devices. The authors concluded that the limited data from the included studies failed to show strong evidence of the efficacy of sound therapy in tinnitus management. The absence of conclusive evidence should not be interpreted as evidence of lack of effectiveness. The lack of quality research in this area, in addition to the common use of combined approaches (hearing therapy plus counselling) in the management of tinnitus are, in part, responsible for the lack of conclusive evidence.

#### Ear Canal Magnets and Electromagnetic Stimulation:

A systematic evidence review published in *BMJ Clinical Evidence* (Savage, et al., 2009; Savage, et al., 2011) concluded that the effectiveness of ear canal magnets and electromagnetic stimulation for tinnitus are unknown.

The systematic evidence review identified two small randomized, controlled clinical trials comparing electromagnetic stimulation to placebo. The first trial (n = 58) found that 15 minutes per day of electromagnetic stimulation significantly increased the proportion of people who had subjective improvements in tinnitus compared to placebo after one week (citing Roland et al, 1993). Based upon subjective responses assessed by a 4-point questionnaire, 14 of 31 subjects assigned to electromagnetic stimulation improved compared to 2 of 23 subjects assigned to placebo (p = 0.0013). The systematic review noted that 4 subjects withdrew from the trial, and that the analysis was not by intention to treat. A second randomized controlled clinical trial (n = 20) used a crossover design and did not report results before the crossover (citing Dobie et al, 1986). The crossover trial found similar effects between electromagnetic stimulation and a placebo device in reducing tinnitus severity. Severity, measured on a scale of 0-7, was reported as less severe in 2 of 20 subjects with the active device versus three of 20 subjects with a placebo device.

The systematic evidence review found one randomized controlled clinical trial (n = 49) that found similar effects between a simple ear-canal magnet and placebo (similar unmagnetized material) in tinnitus symptoms after 4 weeks' treatment (citing Coles et al, 1991). Symptom improvement was reported in 7 of 26 persons with the magnet compared to 4 of 23 persons with placebo.

#### Tinnitus Retraining Therapy:

Tinnitus retraining therapy (TRT) is a neurophysiological approach centering on behavioral retraining of the associations induced by perception of tinnitus. It uses devices similar to tinnitus maskers. These devices, known as white noise generators, produce white noise, and are used over a period of several months to help patients in their habituation of tinnitus. Measurement of the tinnitus match is performed after an audiogram. The patient is asked to identify which of the tones of the audiometer match the tone of the ringing of his or her tinnitus. Examples of measures quantified include pitch, loudness and minimal masking level of the tinnitus. As mentioned, these parameters are then used for tinnitus retraining and for selecting devices, which can produce "white noise" to counterbalance and reduce or eliminate the tinnitus. There are several factors that influence the frequency spectrum of the perceived noise such that the perception of white noise from a white noise generator is unlikely. These factors include (i) the actual spectrum of the emitted noise, (ii) the ear canal resonance of the patient, and (iii) the hearing sensitivity of the patient. Furthermore, a study stated that methodological limitations of the research published to date preclude any claims about the efficacy of TRT at the present time (Wilson et al, 1998). A technology assessment prepared for the Wessex Institute for Health Research and Development (Leal and Milne, 1998) concluded that the available case series are inadequate, owing to problems of methodology, and that there is no evidence to suggest that TRT is effective in the treatment of debilitating tinnitus in adult patients.

Kroener-Herwig et al (2000) stated that there is no published study evaluating TRT using a randomized group design even though this is the only design able to give valid information on the empirical status of a therapy. They concluded that the praise of TRT as the most promising therapy for chronic tinnitus can only be regarded as premature, and the claim of its effectiveness by its advocates await scientific corroboration. Randomized, controlled clinical studies that include no-treatment and placebo groups are needed to ascertain the effectiveness of TRT in the management of patients with tinnitus.

An assessment by the Washington Department of Labor and Industries Office of the Medical Director (Wang, 2004) concluded that “[d]ue to the lack of prospective trials with comparison groups, the efficacy of TRT for subjective tinnitus has not been established. Therefore, TRT is considered investigational and controversial.”

A systematic review of the evidence for tinnitus treatments by BMJ Clinical Evidence concluded that tinnitus training therapy is of "unknown effectiveness" (Savage et al, 2011).

Hiller and Haerkotter (2005) reported that noise generators had benefit in persons with tinnitus. However, post-hoc analysis revealed benefits in a subgroup of tinnitus patients with hyperacusis. They stated that this finding would need to be replicated in a prospective well-controlled study to evaluate sound generators in hyperacusis.

#### Transcranial Magnetic Stimulation:

Clinical, neurophysiological and neuroimaging data suggest that chronic tinnitus resembles neuropsychiatric syndromes characterized by focal brain activation. Low-frequency repetitive transcranial magnetic stimulation (rTMS) has been proposed as a method in treating brain hyperexcitability disorders by reducing cortical excitability. Kleinjung et al (2005) examined the effects of rTMS on patients with chronic tinnitus (n = 14). Increased metabolic activation in the auditory cortex was verified in all patients. After 5 days of rTMS, a highly significant improvement of the tinnitus score was found whereas the sham treatment did not show any significant changes. The treatment outcome after 6 months still demonstrated significant reduction of tinnitus score. The authors concluded that these preliminary results showed that neuro-navigated rTMS offers new possibilities in the understanding and treatment of chronic tinnitus. The findings of this study need to be verified by further investigation with larger sample size and long follow-up.

Pridmore et al (2006) examined the literature and considered the potential for TMS as a treatment for patients with tinnitus. These researchers noted that a small number of studies have suggested that TMS may be effective in the treatment of tinnitus. There is a good theoretical basis and early research evidence suggesting that TMS may have treatment potential in tinnitus. Moreover, they stated that further, larger studies are necessary to ascertain the effectiveness of this approach.

In a randomized, placebo-controlled (sham stimulation) cross-over pilot study, Smith et al (2007) evaluated the effectiveness of neuro-navigated rTMS and its effects on attentional deficits and cortical asymmetry in 4 patients with chronic tinnitus using objective and subjective measures and employing an optimization technique refined in their laboratory. Patients received 5 consecutive days of active, low-frequency rTMS or sham treatment (using a 45-degree coil-tilt method) before crossing over. Subjective tinnitus was assessed at baseline, after each treatment, and 4 weeks later. Positron emission tomography/computed tomography (PET/CT) scans were obtained at baseline and immediately after active treatment to examine change in cortical asymmetry. Attentional vigilance was assessed at baseline and after each treatment using a simple reaction time test. All patients had a response to active (but not sham) rTMS, as indicated by their best tinnitus ratings; however, tinnitus returned in all patients by 4 weeks after active treatment. All patients had reduced cortical activity visualized on PET immediately after active rTMS. Mean reaction time improved ( $p < 0.05$ ) after active but not sham rTMS. The authors concluded that rTMS is a promising treatment modality that can transiently diminish tinnitus in some individuals, but more studies are needed to determine the optimal techniques needed to achieve a lasting response. It is unclear if the improved reaction times were caused by tinnitus reduction or a general effect of rTMS. PET/CT scans immediately after treatment suggest that improvement may be related to reduction of cortical asymmetry associated with tinnitus.

Khedr et al (2008) compared the effect of different frequencies of rTMS (1 Hz, 10 Hz, 25 Hz and sham (occipital, 1 Hz)), given daily over the left temporo-parietal cortex for 2 weeks, on 66 patients with chronic tinnitus randomly divided into four treatment groups. Patients were assessed using the Tinnitus Handicap Inventory (THI), self-ratings of symptoms and audiometric measures of residual inhibition before, immediately after 2 weeks' treatment and monthly thereafter for 4 consecutive months. There were no significant differences in basal measures between the four groups of patients. A 2-factor ANOVA revealed a significant "rTMS" x "time" interaction for all measures. This was because real rTMS produced greater improvement than sham. However, there was no significant difference between the responses to different frequencies of rTMS. The response to rTMS depended on the duration of tinnitus: patients who had tinnitus for the longest period of time were the least likely to respond to treatment. The authors concluded that daily sessions of rTMS over the temporo-parietal cortex may be a useful potential treatment for tinnitus.

In a pilot study, Lee and colleagues (2008) examined the effectiveness of rTMS in veterans with debilitating tinnitus. A total of 8 patients received 5 consecutive days of rTMS (0.5 Hz, 20 minutes) to the left temporo-parietal area. Outcome was measured by means of THI before sessions 1 and 3 and after session 5. Patient 1's THI decreased from 40 to 34 to 26, patient 4 reported a subjective improvement, patient 8 withdrew, and the remaining 5 patients reported no improvement. Side effects included temporary soreness, restlessness, and photophobia. The authors concluded that with these current parameters, rTMS did not improve tinnitus in veterans.

Kleinjung et al (2008) stated that a growing number of studies demonstrate reduction of tinnitus after repeated sessions of low-frequency rTMS and indicate that rTMS might represent a new promising approach for the treatment of tinnitus. Single sessions of high-frequency rTMS over the temporal cortex have been successful in reducing the intensity of tinnitus during the time of stimulation and could be predictive for treatment outcome of chronic epidural stimulation using implanted electrodes. Because most available studies have been performed with small sample sizes and show only moderate effect sizes and high inter-individual variability of treatment effects, further development of the technique is needed before it can be recommended for use in clinical routine. Both patient-related (e.g., hearing loss, tinnitus duration, age) and stimulation-related (e.g., stimulation site, stimulation protocols) factors seem to influence treatment outcome; however, their exact impact still remains to be clarified.

In a Cochrane review, Meng et al (2011) evaluated the safety and effectiveness of rTMS versus placebo in patients with tinnitus. These investigators searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was May 24, 2011. Randomized controlled trials of rTMS versus sham rTMS were selected for this analysis. Two review authors reviewed the titles, abstracts and keywords of all records retrieved; 3 review authors independently collected and extracted data, and assessed the risk of bias of the trials. A total of 5 trials comprising of 233 participants met inclusion criteria. Each study described the use of a different rTMS device that delivered different waveforms at different frequencies. All 5 trials were relatively small studies but generally they demonstrated a low-risk of bias. When considering the impact of tinnitus on patients' quality of life, the results of only 1 study demonstrated a statistically significant improvement in THI scores at 4 months follow-up (defined as a "partial improvement" by the study authors (THI reduction of 21 % to 80 %)) when low-frequency rTMS was compared with a sham control treatment. However, no statistically significant improvement was demonstrated by another 2 studies that considered rTMS at the same frequency. Furthermore, this single positive finding

should be taken in the context of the many different variables which were recorded at many different points in time by the study authors. In accordance with the authors' pre-specified subgroup analysis, they extracted the data from 1 study to consider the differential effectiveness between "lower" low-frequency rTMS (1 Hz) and "higher" low-frequency rTMS (10 Hz, 25 Hz). In doing this they were able to demonstrate a statistically significant difference between rTMS employing a frequency of 1 Hz and the sham group when considering tinnitus severity and disability after 4 months follow-up ("partial" improvement). However, no statistically significant difference was demonstrated between 10 Hz and 25 Hz rTMS, and the sham control group, when considering the severity and disability of tinnitus at 4 months follow-up. When considering tinnitus loudness in patients undergoing rTMS these investigators were able to demonstrate a statistically significant reduction in tinnitus loudness when the results of 2 studies were pooled (risk ratio 4.17, 95 % confidence interval [CI]: 1.30 to 13.40). However, this finding was based on 2 small trials and consequently the confidence interval was particularly wide. No serious adverse effects were reported in any of the trials. The authors concluded that there is very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus. When considering the impact of tinnitus on patients' quality of life, support is from a single study with a low-risk of bias based on a single outcome measure at a single point in time. When considering the impact on tinnitus loudness, this is based on the analysis of pooled data with a large confidence interval. Studies suggested that rTMS is a safe treatment for tinnitus in the short-term, however there were insufficient data to provide any support for the safety of this treatment in the long-term. The authors stated that more prospective, randomized, placebo-controlled, double-blind studies with large sample sizes are needed to confirm the effectiveness of rTMS for tinnitus patients. Furthermore, uniform, validated, tinnitus-specific questionnaires as well as measurement scales should be used in future studies.

Plewnia et al (2012) examined if 4 weeks of bilateral rTMS to the temporal or temporo-parietal cortex is effective and safe in the treatment of chronic tinnitus. In this controlled 3-armed trial, a total 48 patients with chronic tinnitus were treated with 4 weeks (20 sessions) of bilateral continuous theta burst stimulation (cTBS). They were randomized to stimulation above the temporal cortex, the temporo-parietal cortex, or as sham condition behind the mastoid. Patients were masked for the stimulation condition. Tinnitus severity was assessed after 2 and primarily 4 weeks of treatment and at 3 months follow-up with the tinnitus questionnaire and by a tinnitus change score. Audiologic safety was monitored by pure-tone and speech audiometry after 2 and 4 weeks of cTBS. Tinnitus severity was slightly reduced from baseline by a mean (SD) 2.6 (8.2) after sham, 2.4 (8.0) after temporo-parietal, 2.2 (8.3) after temporal treatment of 16 patients each, but there was no significant difference between sham treatments and temporal (CI: -5.4 to +6.7) or temporo-parietal cTBS (CI: -5.9 to +6.3) or real cTBS (CI: -7 to +5.1). Patients' global evaluation of tinnitus change after treatment did not indicate any effects. Audiologic measures were unaffected by treatment. The authors concluded that treating chronic tinnitus for 4 weeks by applying cTBS to the temporal or temporo-parietal cortex of both hemispheres appears to be safe but not more effective than sham stimulation.

In a review on "Repetitive transcranial magnetic stimulation as a treatment for chronic tinnitus", Theodoroff and Folmer (2013) concluded that "Although optimism for the clinical use of rTMS as an effective treatment for tinnitus remains high among many researchers, clinicians, and patients, several key questions and procedural issues remain unresolved. Suggestions for improving rTMS research protocols are described and discussed".

#### Transmeatal Laser Irradiation:

In a prospective, randomized, double-blinded, controlled study, Nakashima et al (2002) assessed the effectiveness of 60-mW laser irradiation in the treatment of tinnitus. A total of

68 ears in 45 patients with disabling unilateral or bilateral tinnitus were included in this trial. The active or placebo laser treatment was administered transmeatally once a week for 6 minutes. Laser irradiation was performed four times during a 4-week period. A questionnaire was administered to evaluate the loudness, duration, quality, and annoyance of tinnitus before and after irradiation. The loudness and pitch match for tinnitus were obtained, and distortion product otoacoustic emissions were also examined. No significant difference was observed between the active and placebo laser groups with regard to outcome of loudness, duration, quality, and annoyance of tinnitus. In 1 patient who received active laser treatment, acute hearing deterioration occurred after the third irradiation. These investigators concluded that transmeatal low-power laser irradiation with 60 mW is ineffective for the treatment of tinnitus.

Tauber et al (2003) presented their findings of a feasibility study on the use of a laser application system in patients with chronic cochlear tinnitus and sensorineural hearing loss (n = 35). The laser TCL-system, consisting of 4 diode lasers ( $\lambda = 635$  to 830 nm) was developed on the basis of dosimetric data from a former light-dosimetric study. The chronic symptoms persisted after standard therapeutic procedures for at least 6 months, while retrocochlear or middle-ear pathologies have been ruled out. The patients were randomised and received 5 single-diode laser treatments ( $\lambda = 635$  nm, 7.8 mW cw, n = 17 and  $\lambda = 830$  nm, 20 mW cw, n = 18) with a space irradiation of 4 J/cm<sup>2</sup> site of maximal cochlear injury. For evaluation of laser-induced effects complete otolaryngological examinations with audiometry, tinnitus masking and matching, and a tinnitus-self-assessment were performed before, during, and after the laser-irradiation. The first clinical use of the TCL-system has been well-tolerated without side-effects and produced no observable damage to the external, middle or inner ear. Changes of tinnitus loudness and tinnitus matching have been described. After a follow-up period of 6 months, tinnitus loudness was attenuated in 13 of 35 irradiated patients, while 2 of 35 patients reported their tinnitus as totally absent. Hearing threshold levels and middle ear function remained unchanged. These researchers stated that further investigations by large double-blind placebo-controlled studies are mandatory for clinical evaluation of the presented TCL-system and its therapeutic effectiveness in acute and chronic cochlear dysfunction.

A systematic review of randomized controlled clinical trials of low-powered laser treatments for tinnitus found no statistically significant difference between laser and placebo (Meehan et al, 2004).

Gungor et al (2008) assessed the effectiveness of laser irradiation in the treatment of chronic tinnitus. This study included 66 ears in 45 patients with chronic unilateral or bilateral tinnitus. A 5 mW laser with a wavelength of 650 nm, or placebo laser, was applied transmeatally for 15 minutes, once-daily for a week. A questionnaire was administered which asked patients to score their symptoms on a 5-point scale, before and 2 weeks after laser irradiation. A decrease of 1 scale point, regarding the loudness, duration and degree of annoyance of tinnitus, was deemed as improvement. The loudness, duration and degree of annoyance of tinnitus were improved, respectively, in up to 48.8, 57.7 and 55.5 % of the patients in the active laser group. No significant improvement was observed in the placebo laser group. The authors concluded that transmeatal, low power (5 mW) laser irradiation was found to be useful for the treatment of chronic tinnitus. The findings of this study need to be validated by larger studies with longer follow-up.

Noble (2008) stated that the various forms of treatment for tinnitus that have been tested in properly controlled trials can be classified as pharmacological, acoustic-physical, and psychological. In clinical trials, no pharmacological agent has been shown to have lasting effect on the presence or severity of tinnitus, although there are promising signs in an animal model. Acoustic devices do not seem to influence tinnitus, although appropriately fitted hearing aids may slightly reduce its prominence. Of physical treatments, cortical

implantation may hold some promise of being effective for tinnitus suppression in selected cases. There was no mention on the use of laser.

In a prospective, randomized double-blind study, Teggi et al (2009) examined the effectiveness of low-level laser therapy on 60 outpatients with tinnitus presenting sensorineural hearing loss in the affected ear. They were randomly divided into two groups: (i) one group received active laser therapy 20 mins a day for 3 months with a 650-nm, 5-mW soft laser (group L), and (ii) the second group received a dummy device which duplicated all aspects of active laser therapy except for the activation of the laser beam (group C). One subject in both groups dropped out due to an increase in tinnitus loudness. Two more patients in each group ceased to comply with the protocol due to familiar problems. The THI was considered the main outcome measure; no statistical difference was detected between the two groups in the THI total score ( $p = 0.97$ ), and its functional ( $p = 0.89$ ), emotional ( $p = 0.89$ ) and catastrophic ( $p = 0.89$ ) sub-scales. Moreover, a visual analog scale for self-perceived loudness of the tinnitus showed no difference between the groups ( $p = 0.69$ ). Regarding psycho-acoustic parameters, the minimum masking level showed no difference ( $p = 0.42$ ), while loudness expressed in sensation level exhibited lower values in group L ( $p = 0.0127$ ). Group L subjects also presented a decreased rate of hyperacusis ( $p = 0.02$ ). No changes were detected in the audiometric threshold in both groups. The authors concluded that soft laser therapy demonstrated no efficacy as a therapeutic measure for tinnitus.

#### Hyperbaric Oxygen Therapy:

In a Cochrane review on the use of hyperbaric oxygen therapy (HBOT) for the treatment of idiopathic sudden sensorineural hearing loss (ISSHL) and tinnitus, Bennett et al (2005) stated that HBOT improved hearing, but the clinical significance of the level of improvement is unclear. Routine application of HBOT to patients with ISSHL is not justified by this review. These investigators noted that more research is needed.

A systematic evidence review of tinnitus treatments by *BMJ Clinical Evidence* concluded that hyperbaric oxygen is of "unknown effectiveness" (Savage et al 2009).

#### Sequential Phase Shift Sound Cancellation Treatment:

Sequential phase shift sound cancellation is a novel treatment for predominant-tone tinnitus. It entails the use of a phase-shift sound cancellation protocol in which a patient's tinnitus is first identified as to frequency and amplitude. Then, a signal, 6 degrees out-of-phase with the identified tinnitus signal, is fed sequentially (6 degrees, 12 degrees, etc.) into the patient's headphones for 30 seconds each for 30 minutes, or until 360 degrees is achieved. Available evidence on the effectiveness of this approach has mainly been in abstract forms (Noik, 2005; Choy and Kaminow, 2005; Lipman et al, 2006). The only published full-length paper on this subject is by Lipman and Lipman (2007) who assessed phase shift treatment for predominant tone tinnitus in a prospective, single-blinded, cross-over study. A total of 61 patients participated in 2 weeks of control and 2 weeks of phase shift treatment. Outcome measures included frequency and intensity matching, pre- and post-treatment tinnitus handicap inventory (THI) scores, and patient diaries. Initial volume comparisons showed a strong relationship between treatment and decrease in tinnitus intensity, with 57 % of patients achieving successful treatment. Thirty-seven percent decreased by one THI grade, 5 % by two. Utilizing patient diaries, 42 % of patients reported periods of complete residual inhibition (CRI) ranging from 1 hour to 7 days (average of 2 days). No periods of CRI were reported in control weeks. The authors concluded that phase shift treatment significantly benefited the majority of patients. These findings suggested that this device may be a valuable tool. They noted that further long-term studies with home therapy are needed.

In a double-blind, cross-over, randomized-controlled trial, Heijneman et al (2012) compared the effectiveness of the treatment of tinnitus with a phase-shifting pure tone to that of the same tone treatment without phase shifting. A total of 22 patients with predominantly tonal tinnitus underwent both intervention and control treatments. Each treatment consisted of three 30-minute sessions in 1 week. The control treatment was identical to the intervention treatment, except that the stimulus was a pure tone without phase shifting. Questionnaires, tinnitus loudness match, and annoyance and loudness ratings were used to measure treatment effects. Pure-tone treatment and phase-shift treatment had no significant effect on tinnitus according to questionnaires (Tinnitus Handicap Index, Tinnitus Reaction Questionnaire, Hospital Anxiety and Depression Scale, and Maastricht Questionnaire), audiological matching procedures, and loudness and annoyance ratings of tinnitus. Furthermore, phase-shift treatment showed no additional significant improvement in comparison with pure-tone treatment. Changes in questionnaire scores due to pure-tone and the phase-shift treatment were correlated. The authors concluded that on average across the group, both treatments failed to demonstrate a significant effect. Both treatments were beneficial for some patients. However, a positive effect was not demonstrated that could be attributed to the periodic shifting of the phase of the stimulus tone.

Thus, there is currently insufficient evidence to support the use of sequential phase shift sound cancellation treatment for tinnitus.

#### Neuromonics Tinnitus Treatment:

The Neuromonics Tinnitus Treatment (NTT) combines the use acoustic stimulation with a structured program of counseling and support by a clinician specifically trained in tinnitus rehabilitation. The acoustic component has been designed to provide stimulation to auditory pathways deprived by hearing loss, engage with the limbic system, and allow intermittent, momentary tinnitus perception within a pleasant and relaxing stimulus, thereby facilitating desensitization to the tinnitus signal. Davis and colleagues (2007) examined the effectiveness of NTT, when enhanced with various modifications since previously reported trials and tested the relative clinical effectiveness of two variations of the approach. In the first, intermittent tinnitus perception was facilitated throughout treatment via the use of a stimulus in which intensity peaks allowed the subjects' tinnitus perception to be completely covered up, whereas in the intensity troughs their tinnitus was briefly discernible. In the second, subjects experienced little tinnitus perception while listening to the treatment for the first 2 months, then experienced intermittent perception. A total of 35 subjects with a predominantly moderate-to-severe level of tinnitus-related distress before treatment were randomly allocated into one of two treatment groups, corresponding to the 2 stage-based variations of the NTT. Subjects were provided with a high-fidelity personal sound player with earphones and an acoustic stimulus that had been spectrally modified according to their individual audiometric profile. They were instructed to use the acoustic stimulus for at least 2 hours per day, particularly at those times when their tinnitus was usually disturbing. Each group had equal amounts of clinician time for education, monitoring, and support. At 2, 4, 6, and 12 months after commencing treatment, both groups displayed clinically and statistically significant improvements in tinnitus distress, awareness, and minimum masking levels as well as loudness discomfort levels. Improvements increased with time over the first 6 months of therapy, at which time 91 % of all subjects across the 2 groups reported an improvement in tinnitus disturbance (as measured by the Tinnitus Reaction Questionnaire) of at least 40 %, with a mean improvement of 65 %. Furthermore, 80 % of subjects at 6 months reported a level of tinnitus disturbance that was no longer clinically significant. There was some indication of a more consistent benefit over 12 months for the group that was provided initially with a high level of tinnitus interaction; however, inter-group differences were not statistically significant. A relation between reported treatment usage

(hours per day) and clinical outcomes was observed, suggesting that a "dosage effect" may apply with the stimulus provided. The authors concluded that this study found that the NNT provides rapid and profound improvements to the severity of tinnitus symptoms and their effect on the subject's quality of life. This was a consistent effect, provided by a treatment that subjects reported as being pleasant to use. Both of the stage-based variations of the treatment that were tested in this study were shown to be successful in achieving these outcomes.

Davis and associates (2008) conducted another clinical study on the effectiveness of NTT. This treatment approach is provided as part of a structured rehabilitation program. In this study, patients who received the customized stimulus (NTT group) reported significantly greater and more consistent alleviation of tinnitus symptoms than did patients who participated in a counseling and support program with and without delivery of a broad-band noise stimulus (Noise + Counseling group and Counseling-Only group, respectively). After 6 months of treatment, 86 % of the NTT patients met the minimum criterion for clinical success, defined as an alleviation of tinnitus disturbance of at least 40 % (as judged by the Tinnitus Reaction Questionnaire score). By contrast, only 47 % and 23 % of the Noise + Counseling and Counseling-Only groups, respectively, reported a successful result according to this criterion. Mean improvements in tinnitus disturbance scores in the NTT, Noise+Counseling, and Counseling-Only groups were 66 %, 22 %, and 15 %, respectively. The differences between the NTT group and the control groups were statistically significant. Significant differences were observed in other clinical outcomes. Patient reports of user acceptability were more consistently positive in the NTT group. It is unclear whether they were overlapping of patients in these two studies.

The major drawbacks of these two studies were (i) small numbers of subjects, and (ii) short-term follow-up (not exceeding 12 months). Moreover, it is unclear whether they were overlapping of patients in these two studies. These findings need to be validated by further investigation.

#### Auditory Perceptual Training:

Hoare et al (2010) stated that auditory perceptual training affects neural plasticity and so represents a potential strategy for tinnitus management. These investigators assessed the effects of auditory perceptual training on tinnitus perception and/or its intrusiveness via a systematic review of published literature. An electronic database search using the keywords 'tinnitus and learning' or "tinnitus and training" was conducted, updated by a hand search. The 10 studies identified were reviewed independently by 2 reviewers, data were extracted, study quality was assessed according to a number of specific criteria and the information was synthesised using a narrative approach. Nine out of the 10 studies reported some significant change in either self-reported or psychoacoustic outcome measures after auditory training. However, all studies were quality rated as providing low or moderate levels of evidence for an effect. The authors identified a need for appropriately randomized and controlled studies that will generate high-quality unbiased and generalisable evidence to ascertain if auditory perceptual training has a clinically relevant effect on tinnitus.

#### Intra-Tympanic Administration of Corticosteroids:

Dodson and Sismanis (2004) reviewed the evidence regarding intra-tympanic treatment for tinnitus and provided the following comments: (i) lidocaine, although effective in decreasing tinnitus, has been largely abandoned because of its severe side-effect profile and need for inpatient administration, (ii) corticosteroids have been associated with few if any side effects, (iii) the good results reported in the literature with intra-tympanic steroids for treating tinnitus of various causes should be viewed with caution, because most are retrospective and uncontrolled studies, (iv) some Meniere's disease patients with tinnitus

may experience tinnitus improvement following intra-tympanic steroids. This treatment may be considered in such patients, especially for those with good hearing, (v) gentamicin is effective in eliminating or reducing tinnitus in a significant number of patients with Meniere's disease and may be considered especially for those with non-serviceable hearing, (vi) further prospective, randomized, controlled studies to evaluate the effect of intra-tympanic perfusion for the treatment of tinnitus are warranted.

In a randomized, prospective, single-blind study, Araújo and colleagues (2005) tested the effectiveness of intra-tympanic dexamethasone injections as a treatment for severe disabling cochlear tinnitus. A total of 36 patients with severe disabling tinnitus predominantly of cochlear origin were randomly assigned to receive intra-tympanic injections of a dexamethasone solution or isotonic saline solution. Under topical anesthesia and after randomization, 36 patients received 0.5 ml intra-tympanic injections once per week for 4 weeks of either a 4 mg/ml dexamethasone solution or saline solution. Five patients were excluded from analysis because they did not complete the treatment or did not return for follow-up. Main outcome measure was improvement of tinnitus measured with a visual analog scale (VAS). The 2 groups were similar in age, sex, tinnitus laterality, measurement of tinnitus intensity on the VAS, and main otologic diagnosis. These researchers considered a 2-point improvement on the VAS to be significant. Twenty-nine percent of the ears in the saline group and 33 % of the ears in the dexamethasone group showed significant improvement immediately after completion of treatment. These measurements were not significantly different from each other. Follow-up varied from 13 to 31 months, and the patients with improved tinnitus returned to the initial measurements over time. The authors concluded that there was no advantage in intra-tympanic injections of dexamethasone over saline solution in the treatment of severe, disabling tinnitus. Both solutions produced a placebo-like improvement.

In a prospective, randomized, placebo-controlled, single-blinded study, Topak et al (2009) examined if intra-tympanically injected methylprednisolone is effective in treating subjective tinnitus refractory to medical treatment. A total of 70 adult patients with subjective tinnitus of cochlear origin were randomly assigned to receive intra-tympanic injection of either methylprednisolone or saline solution. The treatment protocol comprised 3 intra-tympanic injections, 1 per week for 3 weeks. Improvement in tinnitus severity was measured by a self-rated tinnitus loudness scale and by the tinnitus severity index, at baseline and 2 weeks after the last injection. Data for 59 patients were available for analysis. There was no significant difference between the 2 treatment groups regarding age, sex, pure tone average, pre-treatment tinnitus intensity, tinnitus laterality or tinnitus duration. There was a significant post-treatment improvement in self-rated tinnitus loudness scale results in both groups. No significant post-treatment changes in the tinnitus severity index individual and total scores were observed in either group. The most frequently encountered side effects were pain during injection, vertigo, a burning sensation around the ear and in the throat, and a bitter taste. A burning sensation and bitter taste were observed more often in the methylprednisolone group compared with the placebo group. The authors concluded that these findings indicated that intra-tympanic methylprednisolone has no benefit, compared with placebo, for the treatment of subjective tinnitus of cochlear origin refractory to medical treatment.

In a Cochrane review, Phillips and Westerberg (2011) assessed the effectiveness of intra-tympanic steroids on the frequency and severity of attacks of vertigo, on chronic symptoms such as tinnitus, imbalance and hearing loss, and on the progression of these symptoms in patients with definite Meniere's disease or syndrome, as defined by the AAO-HNS Committee. These investigators searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of

the most recent search was January 13, 2011. Randomized controlled trials of intra-tympanic dexamethasone versus placebo in patients with Meniere's disease were selected for this analysis. Two authors independently assessed trial risk of bias and extracted data. They contacted study authors for further information where possible. A single trial containing 22 patients, with a low-risk of bias was included. This trial found that after 24 months, compared with placebo, the use of intra-tympanic dexamethasone demonstrated a statistically significant improvement in vertigo as defined by a respective improvement in functional level (90 % versus 42 %), class (82 % versus 57 %), change in Dizziness Handicap Inventory scores (60.4 versus 41.3) and mean vertigo subjective improvement (90 % versus 57 %). The treatment regime described by the authors involved daily injections of dexamethasone solution 4 mg/ml for 5 consecutive days. These results were clinically significant. No complications were reported. The authors concluded that these findings of a single trial provide limited evidence to support the effectiveness of intra-tympanic steroids in patients with Meniere's disease. This trial demonstrated a statistically and clinically significant improvement of the frequency and severity of vertigo measured 24 months after the treatment was administered. It is important to note that there were a few aspects of the study that the authors were unable to clarify with the study authors.

#### Deep Brain Stimulation:

In a case series with chart review, Shi et al (2009) reported deep brain stimulation (DBS) effects in patients with tinnitus. A total of 7 patients implanted with deep brain stimulation (DBS) systems for movement disorders who also reported having tinnitus were interviewed about their tinnitus conditions. Four were available for testing in a specialized tinnitus clinic with their DBS systems turned off or on. Testing included matching of self-rated and psychoacoustically measured tinnitus loudness to measure the impact of DBS on tinnitus; 3 of the 7 patients reported reduced tinnitus loudness when DBS was turned on. Of the 4 patients tested in the clinic, results indicated that DBS of the ventralis intermedialis nucleus of the thalamus caused decreases in tinnitus loudness in 2 patients with relatively prolonged residual inhibition. The authors concluded that these results suggested that DBS of non-auditory thalamus structures may provide tinnitus relief for some patients. This preliminary findings needs to be validated by well-designed studies.

Cheung and Larson (2010) reported that that application of DBS therapy to a locus of caudate neurons (area LC) can decrease or increase tinnitus loudness perception. The DBS lead traversed through or was adjacent to area LC in 6 Parkinson's disease and essential tremor subjects with concomitant tinnitus who underwent implantation of the subthalamic or ventral intermediate nucleus. In 5 subjects where the DBS lead tip traversed area LC, tinnitus loudness in both ears was suppressed to a nadir of level 2 or lower on a 0 to 10 rating scale. In 1 subject where the DBS lead was outside area LC, tinnitus was not modulated. In 3 subjects with pre-operative and post-operative audiograms, hearing thresholds were unchanged by area LC stimulation. Neuromodulation of area LC may be interrupting perceptual integration of phantom sensations generated in the central auditory system. The authors stated that this new, basal ganglia-based approach to tinnitus modulation warrants further investigation and may be ultimately refined to treat patients with refractory symptoms.

#### Vagal Nerve Stimulation:

Schnupp (2011) stated that recent observations linking the vagus nerve to plasticity in the central nervous system could pave the way to new treatments for tinnitus, one of the most common and intractable disorders of the auditory system. Furthermore, an UpToDate review on "Treatments for tinnitus" (Dinces, 2012) does not mention the use of vagal nerve stimulation as a therapeutic option.

#### Miscellaneous Treatments:

Tao and Chen (2012) evaluated the effects of cochlear implantation (CI) on ipsilateral tinnitus. With standard assessment table and standard testing program, 48 post-lingual hearing-impaired adults aged 18 to 62 years (mean age at implantation: 35.0) were operated at 5 clinical centers from June 2009 to March 2010. There were 23 males (47.9 %) and 25 females (52.1 %). These researchers evaluated the pre- and post-implantation degrees of tinnitus, performed free sound field audiometry and scored speech perception during different periods. Secondary analyses were conducted to examine the correlation between the effects of implantation on tinnitus and hearing or speech perception rehabilitation. Before implantation, there were 16 cases with ipsilateral tinnitus and 32 cases without tinnitus. After implantation, among 16 cases, the outcomes were recovery (n = 6), tinnitus suppression (n = 1) and no change in symptoms (n = 9). The total effective rate was 43.8 %. Among another 32 cases without pre-operative tinnitus, 2 cases developed tinnitus after implantation. The effects of CI on tinnitus were negatively correlated with the course of tinnitus. There was no more correlation with other factors. The authors concluded that CIs have significant therapeutic effects on tinnitus in 43.8 % of implant users. Better efficacies are correlated with a shorter course of tinnitus. However, they stated that tinnitus suppression using electrical stimulation via CI for deafness needs to be further evaluated.

Tavora-Vieira et al (2013) examined the effectiveness of CI in patients with unilateral deafness with and without tinnitus. A total of 9 post-lingually deafened subjects with unilateral hearing loss, with and without tinnitus ipsilaterally, and functional hearing in the contralateral ear were implanted with a standard electrode. Speech perception in noise was tested using the Bamford-Kowal-Bench presented at 65 dB SPL. The Speech, Spatial, and Qualities (SSQ) of Hearing Scale was used to evaluate the subjective perception of hearing outcomes, and the Tinnitus Reaction Questionnaire assessed the effect on tinnitus. All patients were implanted with the Med-El Flex soft electrode, Innsbruck, Austria. They were regularly wearing the speech processor and found it beneficial in improving their ability to hear, particularly in noise. Decrease of tinnitus perception and an improvement of sound localization sounds were also reported by these patients. The authors concluded that in this case series, CI was successful for all 9 patients, with improvement of speech recognition in noise, self-perceived improvement of hearing, and for tinnitus control. Moreover, they stated that several factors such as deafness duration, age of deafness onset, the presence of residual hearing, patient motivation, and the rehabilitation intensity need to be further investigated in order to understand their impact on performance after implantation. (It is unclear how many of the 9 patients had tinnitus)

In a review on "Cochlear implantation for single-sided deafness: The outcomes. An evidence-based approach", Vlastarakos et al (2014) reviewed the current evidence on the effectiveness of CI as a treatment modality for SSD, and/or unilateral tinnitus. Systematic literature review in Medline and other database sources was conducted along with critical analysis of pooled data. The study selection includes prospective and retrospective comparative studies, case series and case reports. The total number of analyzed studies was 17. A total of 108 patients with SSD have been implanted; 66 patients due to problems associated with SSD, and 42 primarily because of debilitating tinnitus. Cochlear implantation in SSD leads to improved sound localization performance and speech perception in noise from the ipsilateral side with an angle of coverage up to (but not including) 90° to the front, when noise is present in the contralateral quartile (Strength of recommendation B). Speech and spatial hearing also subjectively improve following the insertion of a CI (Strength of recommendation B); this was not the case regarding the quality of hearing. Tinnitus improvement was also reported following implant placement (Strength of recommendation B); however, patients need to be advised that the suppression is mainly successful when the implant is activated. The overall quality of the available evidence supports a wider use of CI in SSD following appropriate selection and

counseling (overall strength of recommendation B). It remains to be seen if the long-term follow-up of large number of patients in well conducted high quality studies will confirm the above mentioned results.

Furthermore, an August 2013 Agency for Healthcare Research and Quality's comparative effectiveness review on "Evaluation and treatment of tinnitus" (Pichora-Fuller et al, 2013) indicated that the use of cochlear implants for tinnitus and single-sided deafness is a very recent off-label indication, and indicated insufficient evidence for the use of this and other sound therapies for tinnitus.

In a pilot study, Berninger et al (2006) examined the effect of intravenously administered mexiletine on subjective tinnitus and hearing in 6 patients, who initially responded positively to lidocaine. Distinct mexiletine-induced decreases in tinnitus loudness were demonstrated in 3 subjects, as reflected by maximum VAS level reduction of 34 %, 95 %, and 100 %, respectively. One subject reported change in tinnitus pitch, another one showed a slight (18 % on VAS) tinnitus reduction, and 1 subject disclosed no effect. Side effects were seen only during 1 of 7 infusions. Mexiletine induced shifts in pure-tone threshold, transient evoked oto-acoustic emission, and acoustic reflex threshold, probably reflecting a reversible interference in the function of organ of Corti. The concentration effect relationship remained unclear and no general "therapeutic" level could be identified. The authors concluded that this study confirmed the effect of mexiletine on the auditory function and its potential as a possible therapeutic agent or a model for further development in tinnitus pharmacotherapy.

An UpToDate review on "Treatment of tinnitus" (Dinces, 2014) does not mention the use of mexiletine as a therapeutic option.

Kallio et al (2008) stated that intravenous (IV) lidocaine has been used to ameliorate tinnitus, but in general its effect has been limited. The longer acting local anesthetic ropivacaine may be more effective. These investigators compared ropivacaine with lidocaine for the treatment of tinnitus. A total of 19 randomized, double-blind, cross-over study patients suffering from chronic tinnitus were given a 30-min IV infusion of ropivacaine or lidocaine 1.5 mg/kg at an interval of 2 to 3 months. The intensity of tinnitus was evaluated on THI scale and on the VAS. Plasma ropivacaine and lidocaine concentrations were determined. In both treatments, the infusion decreased the VAS score significantly.

At the end of infusion, a greater than or equal to 50 % reduction in VAS score was observed in 5 patients by ropivacaine and in 1 patient by lidocaine, but this effect was sustained for 1 hour only in 3 patients. However, the THI scores did not differ significantly within or between treatments. On the post-infusion day, 3 patients after ropivacaine and 5 after lidocaine treatment had greater than or equal to 30 % improvement in the THI score. Four weeks later, 1 patient after ropivacaine and 2 after lidocaine had a greater than or equal to 30 % reduction in the THI score. One patient developed seizures soon after ropivacaine infusion from which he recovered uneventfully. His plasma concentration of ropivacaine was 1,817 ng/ml. The highest individual ropivacaine and lidocaine concentrations were 3,483 and 1,680 ng/ml, respectively. The authors concluded that temporary clinically significant alleviation of tinnitus was observed only in a few individuals after both IV ropivacaine and lidocaine.

Hahn et al (2008) performed a retrospective study of patients suffering from chronic unilateral or bilateral tinnitus that was previously ineffectively treated by oral drugs [betahistine (Betaserc), extract of Ginkgo biloba (EGb 761), tanakan (Tebokan), and cinnarizine-dimenhydrinate (Arlevert), singly or in combination]. These researchers divided 150 tinnitus patients (80 men, 70 women) into 7 treatment groups. Treatments consisted of application of intravenous pentoxifylline, lidocaine, or vinpocetine (Cavinton) and combination of these agents with physiotherapy and soft laser. Mean duration (+/-

standard deviation) of tinnitus in these patients was 7.4 +/- 6.0 years; their mean age was 55.6 +/- 12.5 years. The aim of the study was to compare treatment modalities and define their effectiveness for tinnitus relief. The most effective treatment was defined as a combination of Cavinton and physiotherapy. The authors found that pure lidocaine infusion therapy was ineffective. None of the treatment modalities had an objective correlate of improvement, though improvement was reported by a VAS.

Also, an UpToDate review on "Treatment of tinnitus" (Dinces, 2014) states that "Historically, lidocaine, either intratympanic or intravenous, has been found in observational studies to be modestly efficacious in reducing symptoms of tinnitus. However, given the adverse effects of intravenous lidocaine that clearly outweigh any small benefits, lidocaine should not be used in the treatment of tinnitus".

Blasco and Redleaf (2014) noted that in recent years, otologists have begun to place cochlear implants into non-functioning ears after sudden unilateral hearing loss. Patients in these trials demonstrated differing degrees of hearing loss in the un-implanted ear. Few studies have examined the role of implantation in patients with normal hearing in the un-implanted ear. These researchers reviewed the available literature to understand if this practice benefits these patients in terms of tinnitus, sound localization, and speech understanding. Medline, Embase, and Cochrane databases were searched for publications from database inception to June 1, 2013, without restriction of language. A search of multiple medical databases was performed to identify articles reporting cases series of CI for unilateral hearing loss. Subjects were included for analysis only if the course of hearing loss was acute and rapidly progressive, if the loss was severe to profound, and if the contralateral ear had normal hearing. A total of 9 appropriate articles were identified, in which 36 patients met the inclusion criteria. Three meta-analyses were performed: of tinnitus (22 patients); of the lowest signal-to-noise ratio, which still allowed 50 % sentence understanding (16 patients); and of sentence understanding at a fixed signal-to-noise ratio (12 patients). They found that measures of tinnitus reduction and decreased signal-to-noise ratios to still allow 50 % speech discrimination were statistically significantly reduced. Systematic review of subjective changes of tinnitus in 27 patients, speech understanding in 16 patients, and sound localization in 16 patients found 96 %, 100 %, and 87 % improvements, respectively. The authors concluded that CI in unilateral sudden hearing loss with a normal functioning contralateral ear might prove to be an effective therapy. Tinnitus is reduced as is the signal-to-noise ratio, which still allows 50 % speech discrimination. All patients felt that they localized sound better, and most felt that they understood speech better. They stated that further studies should be conducted to compare the success of hearing rehabilitation of CI and traditional modalities such as contralateral routing of signal and bone-anchored hearing aids.

The American Academy of Otolaryngology - Head and Neck Surgery Foundation's clinical practice guideline on "Tinnitus" (2014) provided the following recommendations:

Clinicians should not routinely recommend anti-depressants, anti-convulsants, anxiolytics, or intra-tympanic medications for a primary indication of treating persistent, bothersome tinnitus

Clinicians should not recommend transcranial magnetic stimulation (TMS) for the treatment of patients with persistent, bothersome tinnitus

No recommendation can be made regarding the effect of acupuncture in patients with persistent bothersome tinnitus

Larsen and Ovesen (2014) performed a literature search on tinnitus guidelines and treatment. The authors stated that anti-depressants, melatonin and cognitive behavioral therapy have no effect on tinnitus, whereas sound generators, hearing aids and tinnitus

retraining therapy show some but limited improvement. They stated that national recommendations are needed to ensure a homogenous and optimum offer for all patients.

In a prospective, double-blinded, randomized, placebo-controlled trial, Ngao et al (2014) examined the effectiveness of transmeatal low-power laser stimulation (TLLS) in treating tinnitus. Patients with persistent subjective tinnitus as their main symptom were recruited into the study from the out-patient clinics. The recruited patients were randomized into the experimental group or TLLS+ group (patients in this group were prescribed to use TLLS at 5 mW at 650 nm wavelength for 20 mins daily and oral betahistine 24 mg twice-daily for a total of 10 weeks) and the control group or TLLS- group (patients in this group were prescribed with a placebo device to use and oral betahistine 24 mg twice-daily for 10 weeks). All patients were required to answer 2 sets of questionnaires: (i) the THI and (ii) VAS symptoms rating scales, before starting the treatment and at the end of the 10-week treatment period. The total score of the THI questionnaire was further graded into 5 grades, grade 1 being mild and grade 5 being catastrophic. Wilcoxon-signed ranks test and Mann-Whitney test were used to compare and analyze the THI and VAS scores before and after treatment for each group. Changes with p value of  $< 0.05$  were considered as statistically significant. Chi-square test was used to analyze the change of parameters in categorical forms (to compare between TLLS+ and TLLS-). Changes with p value of  $< 0.05$  were considered as statistically significant. A total of 43 patients successfully and diligently completed their treatment. It was noted that using any condition of the device, TLLS+ or TLLS-, patient's tinnitus symptoms improved in terms of THI scores (TLLS+, p value = 0.038; TLLS-, p value = 0.001) or VAS scores with a change of at least one grade (TLLS+, p value = 0.007; TLLS-, p value = 0.002) at p value  $< 0.05$  significant level. In contrast when TLLS+ group was compared with TLLS- group, no statistically significant result was obtained. In term of VAS scores, there seemed to be no statistically significant improvement in patients' annoyance, sleep disruption, depression, concentration and tinnitus loudness and pitch heard between the two groups. They stated that transmeatal low-power laser stimulation did not demonstrate significant efficacy as a therapeutic measure in treating tinnitus.

In a prospective, double-blind, placebo-controlled study, Dehkordi et al (2015) examined the effect of low-dose laser therapy on chronic cochlear tinnitus. The study population was made up of 66 patients -- 33 who received active laser treatment (case group) and 33 who received inactive dummy treatment (control group). Patients in the laser group received 5 mV with a wavelength of 650 nm for 20 minutes a day, 5 days a week, for 4 weeks. The controls followed the same schedule, but they were "treated" with an inactive device. The degree of tinnitus was evaluated before and after treatment in each group in 3 ways: (i) the TSI, (ii) a subjective 10-point self-assessment scale for tinnitus loudness, and (iii) the Tinnitus Evaluation Test (TET). At study's end, these researchers found no statistically significant differences between the case and control groups in the number of patients who experienced a reduction in TSI values ( $p = 0.589$ ) or a reduction in subjective self-assessment scores ( $p = 0.475$ ). In addition, these investigators did not find any significant reductions in the loudness ( $p = 0.665$ ) and frequency ( $p = 0.396$ ) of tinnitus as determined by the TET. The authors concluded that 5-mV laser therapy with a wavelength of 650 nm is no better than placebo for improving hearing thresholds overall or for treating tinnitus with regard to age, sex, environmental noise level, and the duration of tinnitus.

Claes et al (2014) stated there is evidence that neuroplastic changes in both neural pathways are involved in the generation and maintaining of tinnitus. Neuromodulation has been suggested to interfere with these neuroplastic alterations. In this study these researchers compared the effect of 2 upcoming forms of transcranial electrical neuromodulation: (i) alternating current stimulation (tACS) and (ii) random noise stimulation (tRNS), both applied on the auditory cortex. A database with 228 patients with chronic tinnitus who underwent non-invasive neuromodulation was retrospectively analyzed. The

results of this study showed that a single session of tRNS induced a significant suppressive effect on tinnitus loudness and distress, in contrast to tACS. Multiple sessions of tRNS augmented the suppressive effect on tinnitus loudness but have no effect on tinnitus distress. The authors concluded that the findings of this preliminary study showed a possibly beneficial effect of tRNS on tinnitus and can be a motivation for future randomized placebo-controlled clinical studies with auditory tRNS for tinnitus. They stated that auditory alpha-modulated tACS does not seem to be contributing to the treatment of tinnitus.

Joos et al (2015) noted that recently tRNS applied over the auditory cortex induced a more pronounced effect on tinnitus loudness than transcranial direct current and alternating current stimulation. These investigators performed tRNS over the temporo-parietal cortex in 154 patients with non-pulsatile tinnitus. A total of 119 patients received low-frequency tRNS (lf-tRNS), 19 high-frequency tRNS (hf-tRNS) and 16 whole frequency spectrum tRNS (wf-tRNS). The effect was evaluated by using the numeric rating scale loudness and distress pre- and post-stimulation. This study revealed a significant reduction in tinnitus loudness when lf-tRNS and hf-tRNS were applied as well as a reduction in tinnitus-related distress with lf-tRNS. Moreover, these researchers observed a significantly more pronounced reduction in loudness and distress in pure tone (PT) tinnitus compared to narrow band noise (NBN) tinnitus when hf-tRNS was applied, a difference that could not be obtained with lf-tRNS. The authors concluded that based on these results, tRNS might be a promising treatment option for non-pulsatile tinnitus; however, they cannot yet provide a clear mechanistic explanation for the different results obtained with different types of stimulation, i.e., lf-tRNS, hf-tRNS and wf-tRNS, or with different types of tinnitus, i.e., PT and NBN tinnitus.

Miroddi et al (2015) performed a review to summarize, analyze and discuss the evidence provided by clinical studies evaluating effectiveness of melatonin in the cure of tinnitus.

Due to the fact that there is no satisfactory treatment for tinnitus, clinical research has explored new therapeutic approaches. A search of PubMed, Medline, Embase, Central and Google Scholar was conducted to find trials published prior March 2014 on melatonin in the treatment of tinnitus. Design of the studies, randomization, allocation concealment procedures and diagnostic instruments (scales for tinnitus evaluation) were critical evaluated. A total of 5 clinical studies were included; 3 of them tested effectiveness of melatonin alone, the remaining 2 along with sulpiride and sulodexide, respectively. Considered clinical trials adopted various experimental designs: single-arm, randomized placebo-controlled and randomized placebo-controlled followed by cross-over. These studies were characterized by several methodological weaknesses. The authors concluded that confirmation of melatonin clinical effectiveness in the treatment of tinnitus cannot be given in the light of the biases observed in the considered evidence. Melatonin seems to improve sleep disturbance linked to tinnitus.

In a retrospective study, Ferrari and colleagues (2015) determined the effectiveness of combined treatment with sulodexide (a natural glycosaminoglycan with anti-thrombotic, profibrinolytic and vascular anti-inflammatory properties) and melatonin for the treatment of tinnitus. A total of 30 patients with tinnitus were treated with sulodexide (250 LSU BID, in the morning and in the evening) and melatonin (3 mg in the evening before going to sleep) for 80 days. Evaluations were performed comparing different parameters at basal (T0) and after 40 days (T1) and 80 days (T2) of treatment. The results of THI and acufenometry showed a significant improvement of tinnitus after treatment with sulodexide and melatonin.

In particular, THI total score was reduced from  $37 \pm 20$  to  $27 \pm 18$  ( $p < 0.001$ ) and  $21 \pm 19$  ( $p < 0.001$ ) at T1 and T2, respectively. The percentage of patients with improved symptoms (i.e., reduced score at THI) was 76.7 % at T1 and 90.0 % at T2. Finally a significant improvement was also detected in the tone audiometry test. No side effects were observed during the treatment period. The authors concluded that the combined use

of sulodexide and melatonin confirmed to an important and promising therapeutically option in the tinnitus management.

#### CPT Codes / HCPCS Codes / ICD-9 Codes

##### CPT codes covered if selection criteria are met:

64550 Application of surface (transcutaneous) neurostimulator

##### CPT codes not covered for indications listed in the CPB:

61850 Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical

61860 Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical

61863 Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site(eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array

+61864 each additional array (List separately in addition to primary procedure)

61867 Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site(eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array

+61868 each additional array (List separately in addition to primary procedure)

61870 Craniectomy for implantation of neurostimulator electrodes, cerebellar; cortical

61880 Revision or removal of intracranial neurostimulator electrodes

61885 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array

61886 with connection to 2 or more electrode arrays

61888 Revision or removal of cranial neurostimulator pulse generator or receiver

64568 Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator

64569 Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator

69930 Cochlear device implantation, with or without mastoidectomy

90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	subsequent delivery and management, per session
90869	subsequent motor threshold re-determination with delivery and management
92590	Hearing aid examination and selection; monaural
92591	binaural
92601 - 92604	Diagnostic analysis of cochlear implant
95970	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming
95974	complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour
+95975	complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, each additional 30 minutes after first hour (List separately in addition to code for primary procedure)
+95979	each additional 30 minutes after first hour (List separately in addition to code for primary procedure)
99183	Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session

**HCPCS codes covered if selection criteria are met:**

A4595	Electrical stimulator supplies, 2 lead, per month, (e.g. TENS, NMES)
E0720	Transcutaneous electrical nerve stimulation (TENS) device, two lead, localized stimulation
E0730	Transcutaneous electrical nerve stimulation (TENS) device, four or more leads, for multiple nerve stimulation

**HCPCS codes not covered for indications listed in the CPB:**

C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)

G0277	Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval
G0295	Electromagnetic therapy, to one or more areas, for wound care other than described in G0329 or for other uses
J2001	Injection, lidocaine HCl for intravenous infusion, 10 mg -
L8614 - L8629	Cochlear implant components
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
L8689	External recharging system for battery (internal) for use with implanted neurostimulator, replacement only
L8695	External recharging system for battery (external) for use with implantable neurostimulator, replacement only
V5010 - V5267, V5275, V5298	Hearing aid services and supplies

**ICD-9 codes covered if selection criteria are met:**

386.00 - 386.02	Meniere's disease, unspecified, active cochleovestibular, or active cochlear
388.30 - 388.32	Tinnitus

**Other ICD-9 codes related to the CPB::**

V58.64	Long-term (current) use of non-steroidal anti-inflammatories (NSAIDS)
V58.66	Long-term (current) use of aspirin
V58.69	Long-term (current) use of other medications

**The above policy is based on the following references:**

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