Experimental, Controversial, and Futuristic Treatments for Chronic Tinnitus

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Abstract

Background: Because chronic tinnitus is a condition that negatively impacts the quality of life of millions of people worldwide, a safe and effective treatment for tinnitus has been sought for millennia. However, effective treatments for tinnitus are greatly outnumbered by ineffective strategies, medications, devices, and surgeries that continue to be developed and promoted for the condition.

Purpose: This article describes and critiques experimental, controversial, and potential treatments for chronic tinnitus. The purpose of this review is to provide information that should help patients and clinicians to select tinnitus treatment and management strategies most likely to be effective for each set of symptoms and circumstances.

Research Design: PubMed and MEDLINE databases (National Center for Biotechnology Information, U.S. National Library of Medicine) were searched for the term tinnitus in articles published from 1940 to 2012. Other historical documents and publications were also reviewed as needed for particular topics.

Study Sample: Studies included in this review were selected to represent a sampling of treatment methodologies that have been used for tinnitus.

Data Collection and Analysis: Due to the heterogeneity of the studies reviewed, it was not appropriate to perform a meta-analysis. A selective review of the literature was conducted to summarize and critique published research results.

Results: Most invasive treatments for tinnitus should be avoided because (1) at best, there is scant evidence that any of these treatments is effective, and (2) the risk to patients for most invasive procedures is much greater than the risk posed by the tinnitus perception. Effective and non-invasive treatments for tinnitus include acoustic therapy (which includes hearing aids and other types of environmental sound enrichment); cognitive-behavioral therapy; psychological counseling; hypnosis; biofeedback; and relaxation training. Over-the-counter or prescription medications may be used as needed to facilitate sleep and to reduce anxiety, depression, or obsessive-compulsiveness.

Conclusions: Patients and clinicians should be especially cautious when considering invasive (and potentially harmful) treatments for tinnitus, which is a non-life-threatening symptom. Unless well-designed clinical trials verify that a tinnitus therapy demonstrates effectiveness above and beyond
the placebo effect, consumers should be wary of medications, devices, or procedures promoted as a “cure.” Although a true cure for tinnitus has not yet been found, effective and noninvasive tinnitus management strategies are available now. If progress is made to medically (or genetically) treat sensorineural hearing loss in humans, this breakthrough should also help to simultaneously reduce the perception of tinnitus for many patients.

Key Words: Auditory rehabilitation, management, tinnitus, therapy, treatment

Abbreviations: AlstR/AL = allatostatin receptor/allatostatin; BAHA = bone-anchored hearing aid; CBT = cognitive-behavioral rehabilitation; DBS = deep brain stimulation; ECT = electroconvulsive therapy; FDA = Food and Drug Administration; GABA = gamma-aminobutyric acid; LC = light chain; LTA = left temporoparietal area; MVD = microvascular decompression; RAIC = rostral agranular insular cortex; rTMS = repetitive transcranial magnetic stimulation; TDCS = transcranial direct current stimulation; THI = Tinnitus Handicap Inventory; TMS = transcranial magnetic stimulation; SSRI = serotonin-specific reuptake inhibitor; VAS = visual analog scale

INTRODUCTION

Because chronic tinnitus is a condition that negatively impacts the quality of life for millions of people worldwide, a safe and effective treatment for tinnitus has been sought for millennia. For example, the Ebers Papyrus (an Egyptian medical document originating in 3000 B.C.E.) recommended intraural infusions of balanites oil and frankincense as treatment for a “bewitched ear” (Dietrich, 2004). Medical practitioners in Assyria (sixth century B.C.E.) offered this advice: “If the hand of a ghost seizes on a man and his ears sing, apply herbs, oils and salt through a hollow reed” (Carey, 1988). The famous physician Galen of Pergamon (130–200 C.E.) recommended the following for his tinnitus patients: “Dull the senses with mandrake or opium” (Kraft, 1998). Such potent substances may or may not affect tinnitus directly, but they are likely to distract patients’ attention away from the symptom for a while.

More recent attempts to treat tinnitus have employed a wide variety of methods, including electrical stimulation of the patient’s head; inserting magnets into the ear canals; prefrontal leucotomy; and a plethora of potions and pills that include exotic ingredients such as lyophilized powder of enzymolyzed honeybee larvae (Aoki et al, 2012). In spite of these creative approaches, a true cure for the most common etiologies of tinnitus (damage or degeneration within the auditory system) remains elusive. This review describes and critiques some tinnitus treatments that have been developed or investigated.

Research Design

PubMed and MEDLINE databases (National Center for Biotechnology Information, U.S. National Library of Medicine) were searched for the term tinnitus in articles published from 1940 to 2012. Other historical documents and publications were also reviewed as needed for particular topics.

Study Selection

Studies included in this review were selected to represent a sampling of treatment methodologies that have been used for tinnitus. The purpose of this manuscript is not to be an exhaustive review of tinnitus treatments but, rather, to focus on experimental and controversial treatments for chronic tinnitus.

Data Collection and Analysis

Due to the heterogeneity of the studies reviewed, it was not appropriate to perform a meta-analysis. A selective review of the literature was conducted to summarize and critique published research results.

Results

Some tinnitus treatment methods show potential to offer tinnitus relief, while others lack evidence to support their claims of being beneficial and should therefore be avoided. This is not meant to be an exhaustive review; the article reflects the authors’ professional biases and prerogatives.

ACOUSTIC THERAPY

Acoustic therapy is often a component of effective tinnitus management. One definition of acoustic therapy is “using external sounds to provide relief from tinnitus.” This is not a new concept, as the following examples (recounted by Stephens, 1987) illustrate:

- Alexander of Tralles (525–605 C.E.) suggested that tinnitus sufferers could obtain relief by walking in “sondry places.”
- “Why is it that buzzing in the ears ceases if one makes a sound? Is it because a greater sound drives out the less?” (Salerno School, 12th–13th centuries C.E.)
- Johan Jakob Wepfer (1620–1695) gave this account of one patient’s technique: “He banged two pebbles..."
During the last two centuries, numerous techniques and devices have been developed to deliver acoustic therapy to tinnitus sufferers. Urbantschitsch (1883) used tuning forks; Wilson (1893) tried a telephone transducer; Spaulding (1903) played a violin. Porter and McBride (1916) suggested that tinnitus patients should place a loud ticking clock near their beds. Saltzman and Ersner (1947) recommended hearing aids for tinnitus relief.

The rationale for all of these strategies is the same: increase the level of external sounds in the patient’s environment in order to decrease the patient’s perception of tinnitus. Acoustic therapy has been shown to be an effective method to reduce tinnitus perception or severity (Folmer and Carroll, 2006; Henry et al, 2008). In a quiet environment, the tinnitus signal is prominent, and the level of background sound is low. This phenomenon was demonstrated by Heller and Bergman’s study published in 1953. They asked 80 adults who had normal hearing and no tinnitus to enter a sound booth (one at a time) and make note of the sounds they heard while in the booth. The interior of the booth had a maximum background sound level of 18 dB SPL. While they were in the booth, 75 (94%) of these subjects reported that they heard sounds such as buzzing, humming, ringing, insects, or pulsations. Heller and Bergman (1953) concluded, “It appears that tinnitus is present constantly, but is masked by the ambient noise which floods our environment. This ambient noise level for ordinary quiet living conditions usually exceeds 35 dB SPL and is of sufficient intensity to mask physiological tinnitus which remains subaudible. It would appear, then, that tinnitus will not be eliminated by any treatment but at best can only become subaudible.”

One of the goals of acoustic therapy is to increase the level of background sound in order to decrease the tinnitus signal-to-noise ratio. When background sounds are increased, the tinnitus signal-to-noise ratio becomes smaller; therefore, tinnitus will then be less noticeable and less bothersome or intrusive for most patients. In this issue of JAAA, the article by Hoare et al (2014) describes different methods and strategies of acoustic therapies that can be implemented by clinicians and patients. Here we describe two controversial methods of acoustic therapy that have been promoted recently.

1. The “Inhibitor” ultrasonic tinnitus treatment device (see Fig. 1) is being marketed by the Melmedtronics Company (Colleyville, TX). This battery-powered device is held against the patient’s mastoid and delivers high-frequency stimulation via bone conduction. The idea that high-frequency stimulation (i.e., frequencies near or above the upper range of human hearing, which has a limit of 20 kHz) might provide relief to tinnitus patients was pioneered by the Hearing Innovations company that produced a multifrequency device called “HiSonic.” Originally, HiSonic technology was developed to deliver speech stimuli via ultrasonic bone conduction (Lenhardt et al, 1991) and was promoted as an alternative to cochlear implantation. One major problem emerged: although people with normal hearing or mild-to-moderate hearing loss could perceive speech signals through the device, people with severe to profound hearing loss (the target population) could not. Subsequently, the HiSonic device was promoted as a form of acoustic therapy for tinnitus. Unfortunately, the majority of patients who tried the device disliked the sensations it produced, and they received no relief from tinnitus. A similar fate befell the Aurex-3 device (distributed by ADM Tronics, New Jersey), another version of a high-frequency bone stimulator that did not survive in the tinnitus treatment marketplace. Promoters of the Inhibitor are attempting to rekindle interest in ultrasonic bone conduction for tinnitus, but no well-designed research studies have been conducted to establish or confirm the Inhibitor’s efficacy. Note: These descriptions of the Inhibitor, HiSonic, and Aurex-3 are based on the authors’ experiences with the devices (and with patients who tried them) and therefore reflect the authors’ opinions.
2. A different type of acoustic therapy was described by Reavis et al (2012), who presented a variety of amplitude- and frequency-modulated tones for 3 min at a time to 20 patients with chronic tinnitus. These sounds, in addition to white noise, were presented in a random order to all subjects and at intensities that were just below the tinnitus loudness. The authors concluded: “Our results suggest that, in addition to a traditional masking approach using unmodulated pure-tones and white noise, modulated sounds should be used for tinnitus suppression because they may be more effective in reducing hyperactive neural activities associated with tinnitus.” However, the study described 13 of the 20 subjects as “poor responders” who experienced at most 50% suppression of perceived tinnitus loudness after exposure to any masking sounds. The remaining seven patients were designated as “good responders” who reported 70% suppression of their tinnitus after exposure to masking sounds.

Given these modest results, it is somewhat surprising that Reavis et al recommend using modulated sounds for tinnitus suppression. Independent clinical trials that demonstrate treatment efficacy for this method would help to dispel concerns of bias, given the financial interests in the SoundCure Company disclosed by three of the article’s authors. SoundCure (San Jose, CA) distributes a handheld device that produces modulated tones for use by tinnitus patients (see Fig. 2). According to the company’s Web site (www.soundcure.com),

The Serenade device consists of a handheld acoustic stimuli generator, earphones, and pleasant treatment sounds that are intended to address the underlying cause of tinnitus. A suite of three different types of sounds is included, enabling the audiologist to determine the specific clinical approach that is most likely to be effective for each patient. Unlike most treatment methodologies, Serenade is customizable and can be programmed to meet the unique needs of each patient, day or night. Studies suggest that S-Tones™ may offer immediate relief.

Overstatements of a treatment’s efficacy, even in light of modest research findings, are common in this field and other clinical fields as well. Ioannidis (2011) discusses how conflict of interest can influence medical findings and stresses the importance of validating findings prior to implementing a new treatment. Independent research studies (i.e., performed by researchers who are free of conflicts of interest) should be conducted to validate test results prior to implementing a treatment in clinical practice. Other examples of product development and marketing that occurred before efficacy was fully documented by research include the “Inhibitor” device mentioned previously and a vagus nerve stimulator (developed by Microtransponder, Inc.) described in a later section of this article. Perhaps some of these products are effective treatments for tinnitus, even in a subpopulation of patients. However, well-designed, placebo-controlled clinical trials should be conducted and analyzed before claims of efficacy are made. In order to establish whether a treatment is effective, research must demonstrate that a significant change (clinical or statistical) has occurred that can be attributed to the treatment above and beyond the placebo effect. Performing clinically relevant research is part of conducting evidence-based medicine. By definition, “evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” (Sackett et al, 1996), which leads to an informed decision regarding the results reported in the literature pertaining to a specific treatment prior to implementation.

**PSYCHOLOGICAL INTERVENTIONS**

In this issue of JAAA, the article by Cima et al (2014) describes psychological interventions—such as cognitive-behavioral therapy (CBT) and acceptance and commitment therapy (ACT)—that have demonstrated efficacy for reducing patients’ distress, anxiety, depression, insomnia, and other negative consequences associated with tinnitus perception (Hesser et al, 2011). Andersson and Lyttkens (1999) performed a meta-analysis review on psychological treatments (CBT, relaxation, education, hypnosis, biofeedback, stress management) and reported that these treatments benefit many tinnitus patients. Here we describe two additional psychological interventions that have helped some tinnitus patients.
Hypnosis

Reports of using hypnotherapy to help tinnitus patients began in the 1940s (Pearson and Barnes, 1948) and have been published in every decade since, including the current one (Yazici et al, 2012). Given the fact that hypnotherapy can help to promote relaxation and reduce anxiety (Lee et al, 2007), and might alter neural connectivity between brain regions (Hoeft et al, 2012), it is not surprising that this technique helps tinnitus patients since many studies have established the correlation between tinnitus severity and anxiety/stress (e.g., Folmer et al, 2001). Also, hypnotherapy can be used to augment other behavioral therapies (such as CBT) by encouraging patients to implement more productive coping strategies. Self-hypnosis techniques (Attias et al, 1993) might help to instill a “locus of control” for some tinnitus patients who exhibit a deficiency of this trait.

Is hypnosis more effective than other psychological interventions for tinnitus? Because no large-scale, randomized clinical trials of hypnosis have been conducted with tinnitus patients, it is difficult to gauge the efficacy of the method. Also, different types of hypnotherapy exist and have been used with this population. However, since the procedure carries minimal risk for patients and usually promotes self-improvement and relaxation, hypnotherapy would seem to be more beneficial than harmful in most cases.

Biofeedback

Biofeedback provides information to patients about a physiological measure (such as electroencephalography or muscle tension) while they engage in activities (such as relaxation, meditation, or pleasant visualization) designed to have a positive effect on the physiological characteristic. Reports of clinicians using biofeedback techniques with tinnitus patients date to the 1970s (Grossan, 1976; House, 1978). In the study by House (1978), 41 tinnitus patients attended 12 1 hr sessions with a psychologist who provided instruction on relaxation techniques and strategies. During these sessions, patients received constant feedback via electromyography (EMG) and skin temperature monitoring devices. Successful implementation of relaxation techniques would result in decreased muscle tension and increased skin temperature. Patients were also encouraged to practice the techniques at home between formal sessions in the clinic. House reported that 33 of the patients reported reductions in tinnitus severity immediately after the last therapy session, and 23 patients sustained some improvement 6 to 12 mo later. A majority of patients also reported improvements in general well-being and enjoyment of life and less reliance on anti-anxiety medications. Such positive results are typical of published studies of biofeedback for tinnitus. In this study by House, no control group was included (e.g., one that received relaxation training but no biofeedback). It is likely that 12 1 hr sessions with a psychologist who provides relaxation training would benefit most patients who experience tinnitus and/or anxiety. So we do not know if the biofeedback procedure itself provided additional benefits for these patients. But like hypnosis, biofeedback therapy has helped many patients to increase relaxation and decrease anxiety. Therefore, the procedure is likely to benefit at least a subpopulation of patients with bothersome tinnitus.


OTHER MINIMALLY INVASIVE INTERVENTIONS

Soft Laser

The word soft is used to describe a low-powered laser that can be focused into the patient’s ear canal. In a study by Okhovat et al (2011), a 5 mW medical laser transmitter (Tinnimed, German Medical Laser, Pforzheim, Germany) was connected by a fiberoptic cable and an adapter with a soft silicone tip to the patient’s ear. The laser beam was then directed through the external ear canal and tympanic membrane into the cochlea (i.e., transmeatal). Okhovat et al (2011) irradiated the ear canals of 61 tinnitus patients with a 650 nm, 5 mW soft laser for 20 min per day for 20 consecutive days. The patients’ sensations of tinnitus were measured on a visual analog scale (VAS) before and 2 wk after treatment. The authors reported that the VAS mean difference before and after the treatment was statistically significant ($p < 0.0001$), and the best treatment effect was in the youngest group. Okhovat et al (2011) admit that “the therapeutic mechanism of this method is not completely understood” (p. 33). Siedentopf et al (2007) proposed that laser stimulation might reduce tinnitus by increasing inner ear cell proliferation, adenosine triphosphate (ATP) and collagen production, and secretion of growth factors, and by improving inner ear blood flow and activating hair cell mitochondria that stimulate repair mechanisms.

One criticism of the study by Okhovat et al (2011) is that a placebo control was not part of the research plan. Cuda and De Caria (2008) did include a control group in their study involving 46 tinnitus patients: 26 patients received laser treatment (20 min per day every week day for 3 mo), and 20 patients were assigned to a placebo group. The authors reported that Tinnitus Handicap Inventory (THI) scores improved in the entire sample after treatment, but they changed more significantly in the group receiving low-level laser stimulation. Approximately 61% of irradiated patients had tinnitus...
severity decreased by one class, in comparison to 35% of the placebo group.

However, other published studies failed to find efficacy of low-level laser stimulation for tinnitus. For example, Teggi et al (2009) replicated much of the experimental protocol used by Cuda and De Caria (2008), which included a treatment group and a placebo group of patients. Teggi et al reported that no significant difference was detected between the groups in the THI total score ($p = 0.97$) and the functional ($p = 0.89$), emotional ($p = 0.89$), and catastrophic ($p = 0.89$) subscales. Also, a VAS for tinnitus loudness showed no difference between the groups ($p = 0.69$).

Nakashima et al (2002) conducted a study involving 45 tinnitus patients ($n = 25$ in the treatment group, and $n = 20$ in the placebo group) and used a more powerful (60 mW) soft laser to irradiate the patients’ ear canals. Active or placebo laser treatment was administered transmurally once per week for 6 min; irradiation was performed four times during a 4 wk period. Nakashima et al (2002) reported that no significant difference was observed between the active and placebo laser groups with regard to loudness, duration, quality, and annoyance of tinnitus. In one patient who received active laser treatment, acute hearing deterioration occurred after the third irradiation. The authors concluded that “transmural low-power laser irradiation with 60 mW is not effective for the treatment of tinnitus” (Nakashima et al, 2002, p. 296).

Why did some studies conclude that soft laser irradiation is an effective treatment for tinnitus, while other studies found no efficacy for the procedure? The lack of a placebo control in the study by Okhovat et al (2011) is a serious experimental design flaw that occurs in many tinnitus investigations. While Cuda and De Caria (2008) did include a placebo group in their study, it is possible that “blinding” of research subjects and clinical staff was incomplete. The more rigorous placebo-controlled protocol employed by Teggi et al (2009) reduced clinician bias and influence on research subjects, resulting in no significant treatment effects for this type of laser irradiation.

### Wearable Magnets

Wearable magnets have been touted as treatments for a variety of conditions, including arthritis, diabetes, gout, chronic pain, even cancer (Philpott and Kalita, 2000; Rose, 2001). The devices are available in many shapes and sizes and can be worn as bracelets or necklaces; also, magnetic appliqués can be attached to the skin of the arm, leg, back, or head–wherever relief is desired. Takeda (1987) inserted small round (4 mm diameter, 2 mm thick) magnets embedded in cotton into the ear canals of 56 tinnitus patients. After one week, tinnitus was reduced in 37 patients, did not change in 18 patients, and worsened for one patient. Takeda reported that the beneficial effects lasted at least 3 weeks, and sometimes longer than 9 weeks.

However, a placebo control was not included in the experimental design. In 1991, Coles et al conducted a double-blind, placebo-controlled study of tinnitus patients using the same types of magnets that Takeda employed. Magnets or physically similar but nonmagnetic pieces of metal were mounted on cotton and inserted into the ear canal of patients on the side where tinnitus perception was loudest; 26 patients received magnets, and 23 received nonmagnetic metal “plugs”. Results were obtained after 4 wk (Table 1). Coles et al concluded, “it is self-evident that this line of treatment is insufficiently effective to be clinically worthwhile, except perhaps as a form of placebo treatment, and has to join the long list of claimed treatments for tinnitus that have not stood up to clinical trial” (1991, p. 372).

### Transcranial Magnetic Stimulation (TMS)

A much more powerful magnetic field—delivered to the patient’s head by a technique called transcranial magnetic stimulation (TMS)—is being assessed for its potential to reduce tinnitus perception and severity. TMS involves delivering electromagnetic pulses through a coil that is in contact with the patient’s scalp (see Fig. 3). Ultimately, some of this energy is transmitted through the skull, inducing an electric current that affects the activity of underlying neural tissue. Low-frequency repetitive TMS (1 Hz or less) is known to reduce neural activity in directly stimulated brain regions (Chen et al, 1997; Maeda et al, 2000; Siebner et al, 2003) as well as in structurally connected remote brain regions (May et al, 2007). For this reason, repetitive TMS (rTMS) has been investigated as a possible treatment for disorders related to increased neural activity (Hoffman and Cavus, 2002), including tinnitus. Several different functional imaging studies have shown that, compared to control subjects, people who experience tinnitus have increased activity in the auditory cortex, even in the absence of external auditory stimuli (Arnold et al, 1996; Lockwood et al, 1998; Folmer, 2007). Therefore, applying low frequency TMS to auditory cortex, as well as the dorsolateral prefrontal cortex (De Ridder, Song, et al, 2012), may reduce patients’ perceived severity or loudness of

### Table 1. Effect of Wearable Magnets on Tinnitus (Coles et al, 1991)

<table>
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<tr>
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<th>Magnet group ($n = 26$)</th>
<th>Placebo group ($n = 23$)</th>
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<tbody>
<tr>
<td>Tinnitus improved</td>
<td>7 (27%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>No change</td>
<td>12 (46%)</td>
<td>16 (70%)</td>
</tr>
<tr>
<td>Tinnitus worsened</td>
<td>7 (27%)</td>
<td>3 (13%)</td>
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Transcranial Direct Current Stimulation (tDCS)

Another promising treatment for tinnitus is transcranial direct current stimulation, or tDCS (Vanneste et al., 2013). This procedure involves attaching one end of electrodes to the patient’s scalp and the other end to a current source. Application of electrical current then either increases or decreases the neuronal excitability or activity beneath the stimulating electrode. In one of the first published studies of tDCS for tinnitus, Fregni et al (2006) reported that stimulation of the left temporoparietal area (LTA) resulted in a significant reduction of tinnitus, similar to that produced by 10 Hz TMS. A review of subsequent tDCS studies for tinnitus (Song et al., 2012) indicated that 39.5% of all patients responded to active tDCS with a mean reduction in tinnitus intensity of 13.5%. Active tDCS was found to be more effective than sham tDCS for tinnitus intensity reduction (Hedges’ g = .77, 95% confidence interval = 0.23–1.31). Therefore, Song et al concluded that tDCS may be a promising tool for tinnitus management. To further assess the efficacy of the procedure, the authors recommended implementation of larger randomized clinical trials (RCTs) as well as a comparison between LTA and frontal tDCS electrode placement positions.

MEDICATIONS

The article by Shi et al (2014) in this issue of JAAA describes the role of the physician in tinnitus management. One of these roles is to prescribe medications that might help tinnitus patients by alleviating the severity of associated symptoms such as insomnia, anxiety, depression, or obsessive-compulsiveness. This section will provide an overview of over-the-counter, prescription, and experimental medications that have been advocated or used for tinnitus.

Over-the-Counter Substances

As stated in the introduction of this article, numerous substances have been tried—with minimal success—over the last few millennia by clinicians and patients seeking a cure or treatment for tinnitus. Today, several herbal and homeopathic products are marketed as “tinnitus remedies.” For example, the t-gone company (Henderson, NV) distributes a line of ingestible tablets that are purported to help with tinnitus due to cochlear (or noise) damage, stress, sinus/allergy problems, and tinnitus caused by Ménière’s disease. Ingredients of the tablets include different combinations of tiosinaminum, carbuneum sulphuratum, chininum sulphuricum, pulsatilla vulgaris, cinchona officinalis, belladonna, calcaria carbonica, phosphorus, silica, hydrastis and kalium bichromate. Because such concoctions are not well regulated by governmental agencies, it is difficult to confirm the actual ingredients contained in the tablets and at what dosages. Further, none of these substances has been demonstrated by research to be an effective treatment for tinnitus caused by cochlear damage, noise exposure, stress, Ménière’s disease, or any other etiology of the condition. No clinical trials of t-gone have been published in peer-reviewed literature.

Another company, Arches Natural Products (Salt Lake City, UT), distributes Tinnitus Formula capsules that contain zinc, garlic, and ginkgo biloba extract. The company Web site claims that the capsules were “Specifically formulated for ringing in the ears with clinically proven ingredients for tinnitus.” Arches claims that the capsules have been “recommended by thousands of leading ENT specialists for their patients with tinnitus.” Like the t-gone company Web site, the Arches Web site contains numerous testimonials from “customers” reporting that the products helped them greatly by reducing or eliminating their tinnitus.

Following is a discussion of each of the Tinnitus Formula ingredients to determine if any of them are effective treatments for tinnitus. Several studies assert that tinnitus patients might have lower-than-recommended blood levels of zinc (Ochi et al., 2003; Coelho et al., 2007). However, few placebo-controlled studies of zinc for tinnitus have been conducted. One such investigation, by Paaske et al (1991) concluded that neither zinc supplements nor placebo tablets had any significant effect on tinnitus for 48 patients in the study. Arda et al (2003) also performed a placebo-controlled study of zinc for

![Figure 3. A transcranial magnetic stimulation (TMS) system.](image-url)
tinnitus treatment and did not find any statistically significant results for the supplement. Garlic, the second ingredient in Tinnitus Formula capsules, has not been investigated in a placebo-controlled study of tinnitus. Although it is usually a welcome ingredient in spaghetti sauce, garlic has not been shown to affect cochlear or neural damage that is the root cause of most cases of tinnitus. Linde et al (2001) reviewed herbal medicine used for health-related problems and found insufficient evidence to draw any conclusion for garlic to be used as an herbal remedy. Finally, ginkgo biloba has been touted as an effective treatment for tinnitus and is included in many over-the-counter “remedies.” However, in 2001, Drew and Davies (2001) conducted a double-blind, placebo-controlled trial of ginkgo biloba involving 1121 tinnitus patients. The authors concluded that 50 mg of ginkgo biloba extract given 3 times daily for 12 wk was no more effective than placebo pills in treating tinnitus. Therefore, none of the ingredients in Arches Tinnitus Formula capsules has research support for improving tinnitus symptoms beyond a placebo effect, although the company Web site (www.tinnitusformula.com) proclaims that the ingredients are “clinically proven for tinnitus.”

The placebo effect is an important consideration in assessing the effectiveness of tinnitus treatments because this effect is significant in many clinical trials, especially those involving tinnitus patients (Dobie, 1999). In his review of randomized clinical trials of tinnitus treatments, Dobie (1999) concluded that patients in the placebo group often improved (usually as much as patients did in the active treatment group) because of interactions with clinicians and researchers who took their problems seriously and sought to help them. Therefore, with the exception of many psychological interventions, evaluations of tinnitus treatments should include a placebo group for comparison. As described above, when carefully conducted, placebo-controlled studies of over-the-counter tinnitus “remedies” or ingredients have been conducted, the active ingredients have not performed better than placebos. Some over-the-counter substances (such as those that improve sleep, depression, anxiety, or sinus congestion) might provide some relief or improvement for tinnitus patients and aggravating or coincident conditions (Rosenberg et al, 1998; Megwalu et al, 2006). For example, a recent study conducted in Japan concluded that “the lyophilized powder of enzymolyzed honeybee larvae represents an effective complementary medicine to alleviate depression associated with tinnitus by regulating the activity of the hypothalamus-pituitary-adrenal axis” (Aoki et al, 2012). Until independent studies have been conducted, all of these claims should be considered with caution. Since the underlying mechanism(s) of tinnitus are not completely understood, it seems unlikely any of these substances—including enzymolyzed honeybee larvae—will “cure” tinnitus or facilitate reparations of the underlying causes of the condition.

## Prescription Medications

The severity of tinnitus is positively correlated with depression (Folmer et al, 1999), insomnia (Folmer and Griest, 2000), anxiety (Folmer et al, 2001), and obsessive-compulsive behavior (Folmer et al, 2008). Previous studies demonstrated that effective treatment of these symptoms can help to reduce the severity of patients’ tinnitus (Folmer, 2002). Because most of these comorbid conditions are psychological in nature, a combination of effective psychotherapy and medication can help many patients to improve (Folmer, 2002). However, most of the medications used for this purpose are not prescribed specifically for tinnitus but, instead, for treatment of associated mental health symptoms. It is important for patients to work with clinicians who have appropriate training and experience in behavioral health to find the most appropriate medication and dosage schedule to effectively treat the conditions listed above. Two classes of medications, benzodiazepines and serotonin-specific reuptake inhibitors (SSRIs), were investigated specifically for their effects on tinnitus and are discussed below.

In 1993, Johnson and colleagues conducted a study of the anti-anxiety medication alprazolam, which is in a class of drugs called benzodiazepines (common brand names include Xanax, Valium, Klonopin, and Ativan). The study was undertaken because several patients seen in the investigators’ clinic (Tinnitus Clinic at Oregon Health and Science University, Portland, OR) reported that alprazolam seemed to reduce their perception of tinnitus. In the study by Johnson et al, 17 tinnitus patients took increasing dosages of alprazolam for 12 wk to a maximum dosage of 0.5 mg three times daily; 19 tinnitus patients took lactose pills according to the same schedule for 12 wk. Results indicated a significant reduction in the matched loudness of tinnitus (dB SL) for the alprazolam group, with no similar effect for the placebo group. In fact, the maximum dosage of alprazolam reduced the matched loudness of tinnitus for 13 of 17 subjects in the active treatment group. Also, 11 of these 13 alprazolam patients reported improved sleep patterns, and 10 of these 13 patients experienced reduced anxiety. The placebo patients did not experience improvements in tinnitus, sleep, or anxiety. These findings are not surprising because alprazolam is an anti-anxiety medication that has a sedating effect for many patients. It is likely that the medication reduces patients’ perception of tinnitus via its action as a GABA (gamma-aminobutyric acid) agonist. GABA is one of the major inhibitory neurotransmitters in the human central nervous system. By activating GABA receptors in
the patients’ brain, alprazolam suppressed some of the neural activity responsible for tinnitus perception and also helped patients to relax and sleep.

This study by Johnson et al had a number of design flaws and procedural problems, including small sample size; no measures of tinnitus severity; no formal measures of anxiety; and no long-term follow-up. Also, it was easy for subjects to differentiate between alprazolam and placebo because the lactose pills had no sedating effects. Although alprazolam exhibited some beneficial effects for tinnitus patients, we must ask the following: for which patients do the benefits of taking benzodiazepines (improved sleep; reduced anxiety and tinnitus) outweigh the risks (dependence on medication and sedation)? It is possible for patients to receive some benefits from alprazolam even if they do not take the maximum dosage (0.5 mg three times daily) achieved by patients in the study by Johnson et al. Interested patients should work with their physician to determine if they are good candidates for this medication, which can be used occasionally (daily administration is not required) and in smaller dosages as needed.

A more recent study of alprazolam was conducted among 36 tinnitus patients by Jalali et al (2009). Patients with depressive or anxiety disorders were excluded from the study, as were those who used hearing aids. Results indicated that, compared to placebo, alprazolam did not result in statistically significantly changes in THI score or matched tinnitus loudness. However, there was a significant improvement in VAS tinnitus loudness score for the alprazolam group compared with the placebo group ($p < 0.001$). The fact that patients with depressive or anxiety disorders were excluded makes it difficult to compare the findings in this study to results obtained by Johnson et al.

A different class of prescription medications that has been investigated for tinnitus is SSRIs—drugs that are used to treat depression, anxiety, and obsessive-compulsive behavior. Case reports by Shemen (1998) and Christensen (2001) claimed that use of SSRI medications fluoxetine and paroxetine resulted in “complete resolution” of tinnitus in a total of four patients. Encouraging reports such as these led Robinson et al (2005) to conduct a study of paroxetine in a population of 120 tinnitus patients. In this study, 60 patients took the maximally tolerated dose (up to 50 mg/day) of paroxetine for 31 days, and 60 patients took placebo pills according to the same schedule for 31 days. Results indicated that paroxetine was not statistically superior to placebo on measures including tinnitus loudness matching and the Tinnitus Handicap Questionnaire. Robinson et al concluded, “The majority of individuals in this study did not benefit from paroxetine in a consistent fashion” (2005, p. 981). This negative result probably occurred because of the study design: patients with psychotic or substance use disorders or suicidal ideation were excluded, as were those using psychoactive medications. Consequently, only one tinnitus patient with major depression was included in the study population.

Benzodiazepines and SSRI medications have helped to reduce the severity of anxiety and depression for millions of patients throughout the world. Studies of these medications that excluded patients with anxiety or depression (e.g., Robinson et al, 2005; Jalali et al, 2009) concluded that they were not effective treatments for tinnitus. However, these results should not be interpreted to mean that benzodiazepines and SSRIs are not likely to benefit tinnitus patients. For many patients who experience anxiety and depression in addition to tinnitus, medications such as these in conjunction with effective psychotherapy may help to improve their quality of life and reduce the severity of tinnitus.

**“Off-Label” Use of Prescription Medications for Tinnitus**

In addition to benzodiazepines and SSRIs, many other prescription medications have been tried by clinicians and tinnitus patients. The term *off label* refers to using a medication for a purpose other than that originally approved by the Food and Drug Administration (FDA). For example, a few studies reported that gabapentin (another GABA agonist that was developed as an anticonvulsant) is effective for reducing the perception or severity of tinnitus (Zapp, 2001; Bauer and Brozoski, 2006). However, double-blind randomized controlled trials of gabapentin conducted by Witsell et al (2007) and Piccirillo et al (2007) concluded that gabapentin was not superior to placebo as a tinnitus treatment.

Azevedo and Figueiredo (2005) exhibited creative thinking when they conducted a clinical trial of acamprosate for tinnitus. This study was creative because acamprosate's usual application is a treatment for alcoholism. Specifically, acamprosate helps patients to abstain from alcohol by functioning as a glutamate (excitatory neurotransmitter) antagonist and a GABA agonist in the brain. Because over-activation of glutamatergic pathways and underactivation of GABA-ergic pathways in the central auditory system are thought to play roles in the generation and perception of tinnitus, acamprosate would seem to be a logical choice that might help patients with the condition. In the study by Azevedo and Figueiredo, 23 tinnitus patients received acamprosate, and 18 patients received placebo pills for a period of 3 mo. For an outcome measure, patients rated how “disturbed” they were by tinnitus on a 1–10 scale. At 60 and 90 days postbaseline, the acamprosate group exhibited significant decreases in this measure compared to the placebo group, which did not show significant changes in tinnitus disturbance. Concerns about this study include a small sample
size, a single (and simplistic) outcome measure, and questionable blinding of study participants. A larger, double-blind, randomized controlled trial of acamprosate conducted by W.H. Martin, S. Griest, and Y. Shi (unpublished) at Oregon Health and Science University concluded that the effects of the medication were not significantly different from placebo pills for tinnitus treatment.

Numerous other prescription medications have been tried for tinnitus, with limited success (see Salvi et al, 2009; Savage et al, 2009, for reviews). In our opinion, the medications most likely to help reduce tinnitus-related distress are those that address comorbid symptoms (such as insomnia, anxiety, or depression) when they are present. Also, patients and clinicians should not expect a medication alone to effectively treat tinnitus or any of its symptoms. Because all of these conditions are complex in nature, they require integrated, multidisciplinary management strategies. For example, most tinnitus patients benefit from some sort of acoustic therapy (see the article by Hoare et al [2014] in this issue of JAAA) that can include utilization of hearing aids. Many tinnitus patients also benefit from CBT or other types of psychological interventions that help reduce tinnitus-related distress (see the article by Cima et al [2014] in this issue of JAAA). Prescription medications can thus be viewed as one category of treatment options that may be used in conjunction with other management strategies to help tinnitus patients.

**INVASIVE INTERVENTIONS**

In modern times, one of the most controversial and invasive procedures ever implemented to treat tinnitus was frontal leucotomy, also known as lobotomy (Elithorn, 1953; Beard, 1965). Beard (1965) reported that he performed 20 leucotomy procedures for tinnitus between 1948 and 1957. Prior to surgery, 13 of these patients received electroconvulsive therapy (ECT) for severe depression and other psychiatric disorders. It is now known that ECT can initiate tinnitus for a small percentage of patients who undergo the procedure (Folmer et al, 2011). The leucotomy operations involved drilling holes in the top frontal region of the patient’s skull, then cutting downward through neural tissue, affecting Brodmann’s areas 9 and 10 of the frontal cortex. Regarding outcomes, Beard wrote the following, “of the 19 patients who survived the operation, 11 felt that their head noises were just the same but bothered them less, and 8 felt that they had improved” (1965, p. 30). Beard did not explain what happened to the patient who did not survive surgery, but a 5% mortality rate seems unjustifiable for tinnitus treatment. The author followed up with these patients 5 yr postsurgery and wrote, “only 14 of the 20 patients survived for formal assessment, and of these 14, 5 were very glad they had the operation, 7 were definitely glad, and only 1 regretted it. One patient was unable to say” (Beard, 1965, p. 30). Again, Beard did not explain what happened to the five patients who did not survive 5 yr postsurgery. Beard reported that 12 of the 14 surviving patients found their tinnitus less distressing at the 5 yr follow-up, although the pitch and loudness of tinnitus had not changed for most of them. Beard concluded, “we found that leucotomy gave good results in people incapacitated by psychiatric symptoms reactive to tinnitus, though it is likely that some of these patients could now be helped by drugs not available when these operations were carried out.” Indeed, since the 1950s, development of effective medications for depression, anxiety, and other psychiatric disorders hastened a decline in frontal leucotomy surgeries. A small number of psychosurgeries are still performed today to treat cases of severe mental illness that do not respond to other interventions. These surgeries usually target structures in the limbic system, such as the amygdala, hippocampus, certain thalamic and hypothalamic nuclei, prefrontal and orbitofrontal cortex, and the cingulate gyrus. Functional imaging studies of tinnitus patients have shown abnormal neural activity in the limbic system, suggesting that some of these structures might be associated with certain forms of the condition (Lockwood et al, 1998; De Ridder, Fransen, et al, 2006). Fortunately, we found no additional reports of psychosurgery for tinnitus that were published after Beard’s 1965 article. Below we describe some other invasive treatments that have been implemented for tinnitus.

**Acupuncture**

Insertion of needles into the patient’s skin to treat medical conditions has been practiced in China for more than 3000 yr (Robson, 2004). In Western medicine, reports of using acupuncture to treat tinnitus date to the 1960s (Bischko, 1963), and a clinical trial of the procedure was published in 1982 by Hansen et al. In this double-blind, placebo-controlled trial, the effect of traditional Chinese acupuncture was evaluated among 17 patients with chronic (mean disease duration 5.3 yr), unilateral tinnitus. Each patient received two acupuncture treatments per week for 3 wk. In the last phase of the study, patients who first received active acupuncture switched to the placebo group, and vice versa. After 15 wk, Hansen et al reported that there was no significant difference in tinnitus perception or severity between traditional Chinese acupuncture and placebo (Wilcoxon test, P > 0.05, one-tailed).

Although some recent studies claim that acupuncture is an effective treatment for tinnitus (Wang et al, 2010; Rogha et al, 2011; Jeon et al, 2012), a similar number of reports found no significant treatment effect when active and placebo acupuncture procedures were compared (Hansen et al, 1982; Axelsson et al, 1994; Vilholm...
et al, 1998; Park et al, 2000). This conundrum seems to plague other applications of acupuncture, including its use in pain management. Since the risk of adverse outcomes (e.g., infection, blood vessel or nerve puncture) resulting from professionally applied acupuncture is low, our recommendation to tinnitus patients is this: try it if you are inclined to do so, but have reasonable expectations regarding symptomatic improvement.

Neurectomy

Surgical severance of the vestibular branch of the VIIIth cranial nerve is sometimes performed as a treatment for extreme dizziness that does not respond to other therapies (Colletti et al, 1994; Decat et al, 1997). Unfortunately, tinnitus and hearing loss sometimes result from these procedures (Pappas and Pappas, 1997; Van de Heyning et al, 1997). By contrast, Wazen et al (1997) described a cochlear neurectomy procedure that was performed on two patients who experienced severe tinnitus prior to surgery. Both of these patients also exhibited unilateral profound sensorineural hearing loss in the ear that perceived tinnitus. Because Wazen et al severed the cochlear branch of the VIIIth cranial nerve and preserved the vestibular branch, patients reported a reduction of tinnitus but did not experience dizziness or vertigo. It is important to note that this surgery is recommended only for patients who present with profound sensorineural hearing loss and tinnitus in the same ear. After conducting a retrospective study of surgical procedures and outcomes involving cranial nerves, Silverstein et al (1986) concluded, “when useful hearing is present, a CVN [cochleovestibular neurectomy] is not usually recommended for relief of tinnitus, since the actual cure rates are only 35%. When vertigo is not a complaint, there is currently no surgical procedure known that can be recommended for the treatment of tinnitus” (p. 438).

Microvascular Decompression

Microvascular decompression is a surgical technique that is used to move blood vessels away from nerves on which they are exerting excessive pressure. One of the most common applications of the procedure is to move blood vessels away from the trigeminal nerve in order to relieve symptoms of trigeminal neuralgia (Broggi et al, 2012; Zhang et al, 2012). During the last 30 yr, microvascular decompression of the VIIIth cranial nerve has been performed occasionally to treat chronic tinnitus (Kudo and Ito, 1984; Møller et al, 1993; De Ridder, Vanneste, Adriaenssens, et al, 2010). The majority of published reports state that the procedure reduces or abolishes tinnitus for most patients and usually does not result in adverse effects. However, results from 20 such surgeries described by De Ridder, Vanneste, Adriaenssens, et al (2010) are instructive: the mean preoperative VAS for tinnitus intensity was 7.8 ± 1.5; the mean postoperative VAS was 6.7 ± 2.5, which does not represent a statistically significant change. The mean preoperative Tinnitus Questionnaire (TQ) score was 55.1 ± 17; the mean postoperative TQ score was 55.7 ± 14, which also does not reflect a significant change. Despite this apparent lack of effectiveness, De Ridder (2010) and other neurosurgeons continue to promote microvascular decompression as a viable treatment option for tinnitus. In fact, auditory nerve compression is an exceedingly rare cause of tinnitus; therefore, microvascular decompression surgery for tinnitus should be undertaken in a similarly miniscule number of cases (Folmer, 2010). In 2007, De Ridder et al admitted, “The outcome of operations for tinnitus, moving the blood vessel off the nerve (microvascular decompression operations, MVD) is less successful than microvascular decompression operations for other vascular conflict syndromes” (p. 401). Consequently, clinicians should not recommend MVD procedures for tinnitus unless there is irrefutable evidence that vascular compression of the VIIIth cranial nerve is a causative factor for the symptom.

Implantable Devices

Some implantable devices can improve or partially restore hearing, thereby improving patients’ communication abilities and contributing to increased socialization and quality of life; reduced anxiety, depression, and tinnitus severity. Other types of implantable devices that stimulate cranial nerves or specific brain regions also have the potential to reduce patients’ perception or severity of tinnitus. This section reviews several different classes of implantable devices that have been or could be used to treat chronic tinnitus.

Deep Canal Hearing Aids

Any treatment or procedure that improves patients’ hearing sensitivity is likely to reduce their perception of tinnitus by reducing the tinnitus signal-to-noise ratio. That is why conventional hearing aids benefit many tinnitus patients who also have significant hearing loss: hearing aids improve patients’ hearing and communication abilities and simultaneously make tinnitus less noticeable (Folmer and Carroll, 2006). A recent development in hearing aid technology is the “deep canal” or “implantable” aid distributed by Phonak (Warrenville, IL). This hearing aid (brand name: Lyric) is placed deep into the patient’s ear canal (within 4 mm of the tympanic membrane) by a clinician and can be left in place up to 4 mo (see Fig. 4). Advantages of this device include reduced handling and adjustment; improved sound localization; and external invisibility. Because the Lyric
hearing aid remains in the patient’s ear canal, it constantly increases background sound. For this reason, the device might be of particular benefit to tinnitus patients who need hearing aids. Although no formal studies of the effectiveness of this hearing aid for tinnitus have yet been published, such studies are likely to be conducted and published in the near future.

**Stapes Prosthesis**

Because the cochlea is extremely sensitive to physical vibrations, the force applied during stapedectomy surgery sometimes transfers unnaturally large and harmful vibrations to the inner ear, resulting in permanent hearing loss or tinnitus (Causse et al, 1983; Sancipriano Hernández et al, 1999). Improved surgical techniques such as lasers have reduced the likelihood of this negative outcome (Matković et al, 2003). In fact, successful stapedectomy surgery can help to reduce the patient’s perception of tinnitus. A study of 19 patients with pre-operative severe tinnitus undergoing stapedectomy resulted in 10 patients with complete remission of tinnitus and seven with significant improvement in tinnitus severity (Oliveira, 2007). Two patients had no change, and none reported worsening of tinnitus after surgery. Dost et al (2005) also reported significant improvement in hearing status and tinnitus levels for a majority of 49 otosclerosis patients who underwent stapes prosthesis surgery.

**Cochlear Implant**

Numerous publications have reported that cochlear implantation reduces patients’ perception of tinnitus (Arts et al, 2012; Kim et al, 2013; Kompis et al, 2012). Yonehara et al (2006) reported on 29 cochlear implant candidates, 21 of whom experienced tinnitus before cochlear implantation. When the implant was activated, seven patients (33%) experienced total suppression of tinnitus, and eight (39%) reported partial relief. Cochlear implantation usually improves hearing and tinnitus on the side of implantation in patients with bilateral deafness, but tinnitus sometimes persists, becomes noticeable, or worsens on the side contralateral to the implant. Bilateral cochlear implantation should be considered for some patients who suffer these effects.

**Middle Ear Implant**

The Vibrant Soundbridge (distributed by Med-El, Durham, NC) was approved by the FDA for adults with moderate to severe sensorineural hearing loss who wanted an alternative to acoustic hearing aids. Unlike conventional hearing aids, this device bypasses the ear canal and eardrum by directly vibrating the small bones in the middle ear. No portion of the device is placed in the ear canal. Biesinger (2006) studied eight patients with hearing loss and severe tinnitus who were fitted with a Vibrant Soundbridge. He reported that the device improved hearing and reduced the perception of tinnitus in patients for whom conventional sound stimulation treatments were not helpful.

**Bone-Anchored Hearing Aid (BAHA)**

BAHAs were designed to help people who have chronic inflammation or infection of the ear canal and cannot wear conventional hearing aids, those with conductive hearing loss or with malformed or absent outer ear and ear canals (as occurs in Treacher-Collins syndrome or microtia), and those with unilateral deafness. Holgers and Hakansson (2002) reported that the majority of eight patients with significant hearing loss and tinnitus who received BAHAs stated that sound amplified by the aid helped to make their tinnitus less noticeable.

**Auditory Brainstem Implant**

In the United States, auditory brainstem implants are approved only for patients who suffer from neurofibromatosis type 2. Soussi and Otto (1994) reported that six of seven patients with neurofibromatosis type 2 who received an auditory brainstem implant experienced noticeable tinnitus reduction; the seventh patient reported no effect. Three other patients used the implant only during laboratory testing; one reported complete suppression of tinnitus; one described worse tinnitus; and one reported no effect. More recently, Behr et al (2007) reported that auditory brainstem implants...
improved hearing and reduced the perception of tinnitus for a majority of neurofibromatosis type 2 patients.

**Deep Brain Stimulation (DBS)**

DBS involves surgical implantation of long electrodes into the brain to deliver electrical impulses to specific regions. A stimulator unit is implanted beneath the patient’s skin, usually below the clavicle. An external device is used to control the stimulator, which delivers electrical current through wires to the electrodes. This procedure has provided therapeutic benefits for otherwise treatment-resistant disorders such as chronic pain, Parkinson’s disease, tremor, and dystonia.

Shi et al. (2009) tested four patients who were implanted with deep brain electrodes in the ventral intermedius nucleus of the thalamus for movement disorders. All patients experienced chronic tinnitus, and although the electrodes were not positioned in auditory regions of the brain, two of these patients reported reduced tinnitus loudness when deep brain stimulation was activated. Cheung and Larson (2010) took a more proactive approach to test the efficacy of deep brain stimulation for tinnitus. They enlisted six patients with tinnitus who were scheduled to undergo deep brain stimulation surgery for Parkinson’s disease and essential tremor. Although the final target for electrode implantation was the subthalamic nucleus or the ventral intermediate nucleus, the electrode was paused during surgery in the caudate region to deliver electrical stimulation there. The electrode tip traversed the caudate in five patients for whom tinnitus loudness in both ears was suppressed to a level 2 or lower on a 0–10 rating scale. Tinnitus did not change for one patient in whom the DBS electrode was outside of the caudate region.

These reports are encouraging, but it is important to consider the risks and benefits of this invasive procedure for a symptom such as tinnitus that is not life-threatening. If DBS was performed for tinnitus specifically, how would a target for stimulation in the brain be selected? Based on their experience, Cheung and Larson (2010) might argue for the caudate region, but other candidates could be the auditory cortex (Arnold et al., 1996; Folmer, 2007; Friedland et al., 2007), the medial geniculate region of the thalamus (De Ridder, Vanneste, et al., 2012), the inferior colliculi (Melcher et al., 2009), or the cochlear nucleus in the brainstem (De Ridder, Vanneste, et al., 2012). These vital details need to be investigated and understood before DBS should be recommended as a tinnitus treatment.

**Brain Surface Implants/Stimulation**

Electrode arrays near the surface of the brain also can be used to affect specific neural regions. Subdural electrodes, for example, have been implanted in patients to reduce epileptic seizures or neuropathic pain. De Ridder, Vanneste, van der Loo, et al. (2010) implanted an array of extradural electrodes over secondary auditory cortex in five patients with chronic tinnitus (see Fig. 5). The patients were asked to rate their tinnitus distress and loudness on a VAS before and after 40 Hz tonic and 40 Hz burst (5 pulses at 500 Hz) stimulation. Patients reported significantly better suppression for narrowband noise tinnitus with burst stimulation compared with tonic stimulation. No difference was found between tonic and burst stimulation for pure-tone tinnitus.

Friedland et al. (2007) implanted epidural electrodes over auditory cortex in eight tinnitus patients. Two patients had persistent reduction of pure-tone tinnitus, and six patients had short periods of total tinnitus suppression with continuous stimulation. Significant improvements in the Beck Depression Inventory and tinnitus questionnaires (Tinnitus Reaction Questionnaire and Tinnitus Handicap Questionnaire) were also reported, although more objective measures of tinnitus loudness remained fairly stable.

Since neurosurgery carries significant risks, is implantation of brain surface electrodes a viable treatment for tinnitus? Many questions need to be addressed, for example, Which side of the patient’s brain should receive the implant? De Ridder, DeMulder, et al. (2006) claimed that unilateral tinnitus is generated by contralateral auditory cortex, so his team surgically implanted stimulating electrodes over this area in attempts to suppress tinnitus. However, neural imaging studies by Arnold et al. (1996), Folmer (2007), and other researchers demonstrated that the perception of tinnitus is sometimes associated with activity in ipsilateral auditory cortex. Therefore, the optimal location for cortical stimulation remains uncertain.

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Figure 5. Diagram of a brain stimulation system.
### Vagus Nerve Stimulation

The FDA approved the use of vagus nerve stimulation as an adjunctive therapy for partial-onset epilepsy in 1997 and for treatment-resistant depression in 2005. Researchers associated with MicroTransponder Inc. in Dallas, TX, recently published a study stating that electrical stimulation of the vagus nerve "completely eliminated the physiological and behavioural correlates of tinnitus in noise-exposed rats" (Engineer et al, 2011, p. 101). This publication and subsequent media reports generated a great deal of interest in vagus nerve stimulation among clinicians, researchers, and tinnitus patients, but we must remember that the original experiments were conducted on rats. It seems reasonable to question whether the rats truly experienced tinnitus and what effect vagus nerve stimulation had on their supposed tinnitus.

Engineer et al (2011) hypothesized that vagus nerve stimulation eliminated the perception of tinnitus in rats, but they do not know if stimulation directly affects the perception of tinnitus at all. Because the vagus nerve has such wide-ranging roles and paths of innervation in the body (human and rat), stimulating it will produce a variety of effects. Some of the efferent effects (bronchoconstriction, reduced heart rate, and increased gastrointestinal tract activity) are predictable, and might affect the ways in which patients perceive or react to tinnitus. The afferent effects of vagus nerve stimulation on central nervous system activity are less well known but could affect patients' mood, disposition, motivation, and, indirectly, ways in which they perceive or react to tinnitus.

Although the FDA approved vagus nerve stimulation for treatment-resistant depression, a randomized controlled trial of 235 patients by Rush et al (2005) concluded that no definitive evidence of efficacy for the method was apparent. In light of this finding, we should be wary of initial reports that proclaim the efficacy of vagus nerve stimulation for tinnitus. Of note, these reports were generated by scientists employed by a company that is developing devices for commercial distribution. The article by Engineer et al (2011, online, under "Competing financial interests") states, "[Author] N.D.E. is a full-time employee of MicroTransponder Inc (Austin, Texas), which develops therapies using neurostimulation. [Author] M.P.K. is a consultant and shareholder of MicroTransponder Inc." On the day *Nature* published the online letter by Engineer et al, MicroTransponder Inc. released a media announcement titled, "*Nature* Study Shows That Nerve Stimulation Therapy Can Eliminate Tinnitus in an Animal Model." The company Web site also states that MicroTransponder is developing an implantable system "for a pipeline of additional indications based on Vagus Nerve Stimulation, including stroke rehabilitation, tinnitus, and anxiety." Companies disseminating media releases or developing new products is standard practice. However, it is essential that independent research is conducted prior to corporations (or their employees) making claims as to benefits of their products.

One problem is inherent with all implanted electronic devices: they do not last forever. Eventually, the device will stop functioning because of aging components, failing electronics, or encroachment of the patient’s tissues/fluids, sometimes necessitating device replacement or removal. Researchers, clinicians, and medical device companies continue to develop and test various types of implants that strive to improve hearing and reduce the perception of tinnitus, but patients should thoroughly explore noninvasive strategies for tinnitus relief before undergoing surgery, which includes a hospital stay and associated expenses, especially for implantation of experimental devices. We all look forward to technological advances, but we should not allow patients' zeal for a quick fix to put them at risk for unproven and potentially harmful procedures.

### FUTURE THERAPIES

As we stated earlier, any treatment or procedure that improves patients’ hearing sensitivity is likely to reduce their perception of tinnitus by reducing the tinnitus signal-to-noise ratio. A current line of investigation that aims to restore sensorineural hearing loss is “hair cell regeneration.” Usually, hair cells in the mammalian cochlea do not regenerate if they have been lost due to aging or disease processes or are irreparably damaged by exposure to ototoxic substances or excessively loud sounds. In the 1980s, Cotanche (1987) and Cruz et al (1987,) among others, demonstrated that elements of hair cells in the cochleae of some birds can regenerate after severe damage by ototoxic compounds and loud sound exposure. During the last 25 yr, laboratories around the world have studied this phenomenon in birds (see Ryals et al, 2013, for a recent review), and several investigators have attempted to induce regeneration of hair cells or auditory neurons in the mammalian cochlea. For example, in China, Yang et al (2012) used a viral vector to deliver *Atoh1* (a gene critical for hair cell differentiation) into the cochleae of guinea pigs that were exposed to loud sounds. Scanning electron microscopy revealed that damaged/lost stereocilia bundles were repaired or regenerated after *Atoh1* treatment. In England, Chen et al (2012) implanted human embryonic stem cells into the cochleae of gerbils that served as models for auditory neuropathy. The investigators reported that stem cells were able to differentiate into hair-cell-like cells and auditory neurons that displayed expected electrophysiological properties. Moreover, transplantation of stem cells resulted in significant improvements in the gerbils’ auditory-evoked response thresholds. If any
of the various methods now being studied eventually succeeds in restoring functional hair cells (and hearing) in humans, the treatment should also help to reduce the perception of tinnitus for many individuals who experience this symptom in conjunction with hearing loss.

In addition to treatments designed to restore sensorineural hearing loss, several other procedures are being investigated that might someday be used to reduce patients’ perception of tinnitus.

Genetic Therapy: Viral Vector Inhibition of Neural Activity

Because the generation and perception of tinnitus is often associated with superfluous neural activity, procedures that can suppress such activity in narrowly targeted regions of the central auditory system have the potential to be effective treatments for tinnitus. One such procedure used a viral vector to deliver the gene for the light chain (LC) fragment of tetanus toxin (that induces synaptic inhibition by preventing the release of synaptic vesicles) to discreet regions of the midbrain in rats (Zhao et al, 2006). Expression of the LC gene inhibited the increase in startle amplitude seen with the control viral infection, and blocked context-dependent potentiation of startle induced by fear conditioning in treated rats. A different research group (Nielsen et al, 2012) used a viral vector to deliver an allatostatin receptor/allatostatin (AlstR/AL) system (which has previously been shown to induce inactivation of neurons in vivo) to a region of visual cortex in macaque monkeys. Expression of the AlstR/AL system resulted in suppression of a visual detection task by treated monkeys.

Jasmin et al (2003) described yet another mode of genetic therapy that affects neural activity: locally increasing GABA by using an enzyme inhibitor or gene transfer mediated by a viral vector inhibited activity in the rostral agranular insular cortex (RAIC) of rats. Selectively manipulating GABA(B)-receptor-bearing RAIC neurons produced hyperalgesia or analgesia through projections to the amygdala, a brain region involved in pain and fear.

Taken together, these genetic therapy methods have the potential to help tinnitus patients by (1) reducing neural activity responsible for tinnitus generation and perception and (2) reducing patients’ negative reaction to tinnitus (including fear and anxiety). Of course, many years of additional research are required before these techniques can be applied in human populations.

Optogenetics

Kokaia and Sørensen (2011) described optogenetics as a new method of controlling neural activity by delivering light impulses to specific brain regions. Derived from microbial organisms, opsin genes (encoding light-activated ion channels and pumps) can be genetically targeted into specific neural populations using viral vectors. When exposed to light with the appropriate wavelength, action potentials can be triggered in specific populations of neurons, and inhibition of action potentials can be induced in other neuronal populations, thus allowing for powerful control of neural activity. Restoration of dopamine-related movement dysfunction in Parkinson’s disease, amelioration of blindness, and suppression of neural activity associated with tinnitus are but a few potential applications for this new procedure.

Targeted Drug Delivery

GABA agonists, such as benzodiazepine medications or gabapentin, help some patients by reducing the perception or severity of tinnitus. Lidocaine has also provided relief for tinnitus patients (Marzo et al, 2004; Kallio et al, 2008), although its intravenous delivery and relatively short duration of action limit its practical use. Another problem that plagues medications for tinnitus is their lack of specificity for particular neural targets. In fact, medications such as benzodiazepines, gabapentin, and lidocaine have effects—including unwanted side effects—throughout the patient’s brain and body. Jain (2012) describes a potential solution: nanoparticle-based methods that could enhance and improve drug delivery to the brain. When perfected, these methods could provide delivery of effective medication to specific brain sites to reduce the perception and severity of tinnitus. At the same time, negative side effects and effective dosages of beneficial medications could be reduced.

CONCLUSIONS

Fortunately, most people who perceive chronic tinnitus do not require any treatment interventions for the condition. However, effective and noninvasive management strategies are now available for patients who require them (Andersson and Lyttkens, 1999; Henry et al, 2008, 2009; Hesser et al, 2011; Cima et al, 2014; Hoare et al, 2014) even though a true “cure” for tinnitus has not yet emerged. Duckro et al (1984) stated, “As with chronic pain, the treatment of chronic tinnitus is more accurately described in terms of management rather than cure” (p. 460). This is an important concept for patients and clinicians to understand because most cases of chronic tinnitus (which are associated with sensorineural hearing loss) are likely to persist. Our goal should be to help patients obtain relief from the condition so their quality of life improves and is not affected by the symptom.

Effective tinnitus management strategies described in this issue of JAAA and elsewhere can help patients to reduce their negative reaction to tinnitus; reduce the percentage of time they are aware of or bothered by
tinnitus; gain more control over their tinnitus; reduce anxiety, depression, and insomnia; and reduce tinnitus severity and its negative impact on their lives. Regarding new treatments for tinnitus that will continue to appear in news articles and other media: let the patient beware, because if it seems too good to be true, it probably is. Invasive treatments—especially surgical procedures—should be considered with extreme caution, and a risk/benefit assessment should be conducted before clinicians and patients decide to implement such procedures. When possible, studies of tinnitus treatments should adhere to the requirements of randomized clinical trials (Dobie, 1999) and should include a well-designed control condition to distinguish treatment effects from placebo effects. The great majority of clinical trials (Dobie, 1999) and should include a well-designed control condition to distinguish treatment effects from placebo effects. The great majority of clinical trials that have been conducted for tinnitus treatments suffer from several experimental design flaws, including lack of appropriate controls; lack of adequate sample size; absence of valid outcomes measures; lack of monitoring participant compliance during the study; and inadequate inclusion/exclusion criteria for participants.

Recently, an international consortium of researchers made the following recommendations to facilitate improvement and standardization of tinnitus clinical trials (Landgrebe et al, 2012, p. 119, table 2):

- **Trial planning**
  - Clear formulation of the research question
  - Choice of adequate trial design
  - Definition of one or more main outcome measure(s) (i.e., a validated tinnitus questionnaire)
  - THI should be included in every trial at least as secondary outcome to improve interstudy comparability
  - Sample size estimation based on power calculations (e.g., based on data from pilot studies)
  - Ethical approval
  - Informed consent
  - Establishment of a statistical analysis plan
  - Registration in a clinical trials registry

- **Study performance**
  - The clinical trial should be performed according to good clinical practice (GCP) and CONSORT guidelines

- **Reporting of results**
  - All clinical trials should be published
  - Results should be reported according to CONSORT guidelines

Because of the heterogeneity exhibited by tinnitus patients and their symptoms, tinnitus treatment studies should include as many participants as possible to allow meaningful analyses of subgroups that do or do not respond favorably to specific treatment methods. Due to the variability seen in the tinnitus population, it is important to perform statistical analyses to detect such subgroups and to evaluate how they affect outcomes or respond to a particular treatment. Also, greater standardization of tinnitus outcome measures would facilitate more meaningful comparisons of treatments for the condition.

**REFERENCES**


