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PHARMACOLOGICAL TREATMENTS FOR TINNITUS: NEW AND OLD

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Abstract

Subjective tinnitus, the phantom ringing or buzzing sensation that occurs in the absence of sound, affects 12–14% of adults; in some cases the tinnitus is so severe or disabling that patients seek medical treatment. However, although the economic and emotional impact of tinnitus is large, there are currently no FDA-approved drugs to treat this condition. Clinical trials are now underway to evaluate the efficacy of N-methyl-d-aspartate (NMDA) and dopamine D_2 antagonists, selective serotonin reuptake inhibitors (SSRIs), γ-aminobutyric acid (GABA) agonists and zinc dietary supplements. Previous off-label clinical studies, while not definitive, suggest that patients with severe depression may experience improvement in their tinnitus after treatment with antidepressants such as nortriptyline or sertraline. A small subpopulation of patients with what has been described as “typewriter tinnitus” have been shown to gain significant relief from the anticonvulsant carbamazepine. Preliminary studies with misoprostol, a synthetic prostaglandin E1 analogue, and sulpiride, a dopamine D_2 antagonist, have shown promise. Animal behavioral studies suggest that GABA transaminase inhibitors and potassium channel modulators can suppress tinnitus. Additionally, improvements in tinnitus have also been noted in patients taking melatonin for significant sleep disturbances. Like other complex neurological disorders, one drug is unlikely to resolve tinnitus in all patients; therapies targeting specific subgroups are likely to yield the greatest success.

INTRODUCTION

Tinnitus, from the Latin word *tinnire*, refers to a condition in which a patient experiences a ringing, buzzing or hissing auditory sensation in the absence of an external sound. Tinnitus is broadly classified as being either objective or subjective. The objective form, which is rare, refers to a condition in which a real sound is generated by an internal biological activity, such as vascular turbulence or pulsations or spasm of the muscles in the middle ear, Eustachian tube or soft palate. Subjective tinnitus, the most common type and the subject of this review, refers to a phantom auditory sensation for which no objective sound can be identified.

Individuals who experience severe and disabling tinnitus often seek medical treatment from an otologist, neurologist or psychiatrist with the hope of finding a drug or surgical treatment that can completely switch off their tinnitus and bring back silence. Disappointment and disbelief set in when patients are told by their physician that they must learn to live with it or

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try nonmedicinal approaches involving some form of sound therapy and counseling. While sound therapy and counseling have been found to reduce the severity of tinnitus, often by reducing the emotional or psychological impact, many patients would prefer a “magic pill” that completely abolishes their tinnitus in a matter of hours or days. This review highlights some of the recent pharmacological studies that have been carried out with a variety of agents in the treatment of tinnitus.

PREVALENCE, CHARACTERISTICS AND IMPACT OF TINNITUS

Prevalence

Most individuals at one time or another experience transient tinnitus lasting seconds or minutes; however, others experience long-lasting tinnitus that can persist for a lifetime. The prevalence of tinnitus among those over 65 years of age ranges from 12% to 15% (1–6). Approximately < 1% of the population suffers from severe, debilitating tinnitus that negatively impacts sleep, concentration, work and quality of life, and which requires medical treatment or counseling. Tinnitus occurs roughly equally in females and males (7, 8). As with most disorders, the prevalence of tinnitus increases with age and peaks at around 60–70 years (7).

In 2005, it was estimated that the potential market in the U.S. for tinnitus treatment was approximately $10 billion (9). The Veterans Administration Benefits Report ranked tinnitus as the second most prevalent service-related disability. Among those who began receiving benefits in 2006, tinnitus was ranked first among service-related disabilities at 9.7% of the total (http://www.vba.va.gov/bln/21/). In 2005, the annual compensation for tinnitus-related disability was $418 million. The economic impact of this disabling disorder, combined with the growing number of noise-exposed combat personnel and the swelling ranks of elderly individuals with tinnitus (10, 11), has generated renewed interest in finding therapeutic compounds that can suppress or manage tinnitus.

Perceptual characteristics of tinnitus

A little over half of tinnitus patients perceive the phantom sound as coming from inside the ear (tinnitus aurium), suggesting that tinnitus might originate in the inner ear. Others report that the phantom sound is located inside the head (tinnitus cerebri), raising the possibility of a central origin (12, 13), while a few patients perceive the phantom sound as coming from outside the head. Approximately 60% of patients experience bilateral tinnitus, while the remainder hear the sound in just one ear (14).

Patients often undergo detailed audiometric and psychoacoustic evaluation to assess the status of the auditory pathway. The pure- tone audiogram, which identifies the frequencies where hearing is impaired, is an important procedure, as tinnitus is generally associated with hearing loss. In younger individuals hearing loss is most often associated with noise exposure, while in older individuals it is often associated with age-related hearing loss or presbycusis. The prevalence of tinnitus steadily increases with the degree of age-related hearing loss (7). Despite the frequent association between hearing loss and tinnitus, many individuals with hearing loss do not experience tinnitus. Conversely, some individuals with normal hearing experience tinnitus. The definition of “normal” hearing, however, can be misleading, because most hearing tests are only performed at octave intervals from 125 to 8000 Hz. It is conceivable that these “normal” listeners may actually have undetected hearing loss at interoctave intervals, or hearing loss between 8000 and 20,000 Hz, where hearing is seldom evaluated, or other auditory disorders that are not detected by an audiogram. Clinical trials that assess the efficacy of drugs used to treat tinnitus often use psychoacoustic tests to determine if the loudness, pitch or other qualities of the tinnitus

change as a result of treatment. In some individuals, the perceptual qualities of tinnitus may fluctuate from morning to evening or from day to day, while in others the tinnitus remains stable over time (15). If the patient's tinnitus fluctuates, it is important to have several baseline measurements prior to the start of treatment.

The pitch and spectral qualities of tinnitus vary from one individual to the next, but the most common descriptors used are those of ringing, buzzing, hissing or whistling (16). Because the auditory system is organized tonotopically such that different frequencies activate different anatomical locations in the auditory pathway (similar to a piano keyboard), the pitch and spectral qualities of the tinnitus may provide clues regarding the neurons that trigger the phantom sensation. The pitch or spectral qualities of tinnitus are often located in the region of maximum hearing loss or at the boundary between normal and abnormal hearing (17, 18). These results suggest that the neurons responsible for the perception of tinnitus may be located at the edge or boundary of maximum hearing loss (19).

Loudness, a perceptual phenomenon, is most closely related to sound intensity, a physical measure assessed in units of decibels (dB). Loudness measurements of tinnitus are often obtained with a 10-point visual analog scale, with a score of 10 being very loud and a score of 1 being soft. When patients are asked to rate the subjective loudness of their tinnitus, the average loudness rating is ~6.3, suggesting that the phantom sound is moderately loud (20). Other approaches estimate tinnitus loudness by having the subject adjust the level of an external sound so that it matches the perceived loudness of their tinnitus. In most cases, the tinnitus is matched to an external tone less than 10 dB above the threshold of hearing (< 10 dB sensation level, or 10 dB SL). These low dB SL values may suggest that the tinnitus is not very loud; however, such results may be misleading because dB SL is a measure referenced to the individual's threshold of hearing at that frequency. If a patient has a 40-dB hearing loss and matches the loudness of the tinnitus to 10 dB SL, the sound level would be 50 dB HL, i.e., 50 dB above the normal threshold for hearing at that frequency. Additionally, when a patient suffers from hearing loss, they often experience loudness recruitment, i.e., the loudness of a sound increases rapidly once the sound level exceeds the patient's threshold.

Masking, the ability of one loud sound to cover up a less intense sound, has been used as a treatment for tinnitus, allowing the patient to voluntarily escape from the tinnitus (21, 22). The minimum masking intensity provides an objective method of assessing the loudness of tinnitus. Masking can be expressed in dB SPL (sound pressure level), an acoustic measure, or in terms of dB SL, the sound level relative to the subject's threshold. The minimum masking level can be used to assess the severity of tinnitus (23) and to evaluate the ability of a drug or devices to ameliorate tinnitus severity (24–27). In many cases, tinnitus can be masked at relatively low intensities; in others, high intensities are required, and in a few cases, the tinnitus is unmaskable or made worse by external sounds (16, 28, 29). Masking also provides insights into the neural origins of tinnitus. When a real tone is presented to one ear, it is easily masked by sounds presented to the same ear, but difficult to mask by sounds presented to the opposite ear (30). In contrast, when the phantom sound of tinnitus is perceived in one ear, it can usually be masked by a sound presented to the same ear or the opposite ear (31, 32). One interpretation of these finding is that the neural generator for tinnitus resides in the central auditory system where neural responses from the two ears can interact with one another, rather than in the inner ear where the neural responses are largely independent. Another striking difference between a real sound and tinnitus is that the masker sometimes becomes less effective in covering up the tinnitus the longer it is presented, whereas masking of external sounds remains relatively constant over time (33, 34).

Emotional and psychological responses to tinnitus

A patient's emotional or psychological response to tinnitus can vary from one individual to the next, even among patients whose tinnitus is similar. Consequently, it is important to determine how a drug affects a person's social or emotional response to tinnitus, as well as its perceptual qualities. Frequently used questionnaires for assessing a patient's reaction to tinnitus are the Tinnitus Handicap Inventory, Tinnitus Handicap Questionnaire and Tinnitus Reaction Questionnaire (35–38). These questionnaires focus on issues related to the degree of handicap, sleep, social interactions, emotion, concentration, depression and annoyance of tinnitus. Drugs used to treat tinnitus should either reduce the tinnitus perception or the emotional response, and ideally both.

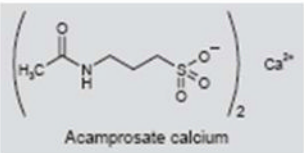
Tinnitus classification

Subjective tinnitus is associated with many different diseases and disorders, and it sometimes emerges as a side effect of medications used to treat other diseases (39). Attempts have been made to classify different forms of tinnitus based on the site of lesion, the patient's description, the clinician's observations, the perceptual characteristics, causation, neurophysiological characteristics, response to treatment and various combinations of these factors (12, 40–43). While none of the classification schemes is widely accepted, there is evidence that certain types of tinnitus may respond well to a particular type of drug therapy (44–47).

DRUG THERAPY FOR TINNITUS: PHARMACOLOGICAL STUDIES

Although tinnitus is a significant health and economic problem, there are no FDA-approved drugs to treat tinnitus (9) and few drugs reliably suppress or eliminate chronic tinnitus in the majority of patients (48–50). The lack of drug therapies is due in part to a limited understanding of the biological basis of tinnitus, the lack of an accepted tinnitus nosology, the heterogeneity of the tinnitus population, the wide range of medical conditions that appear to cause tinnitus and the huge cost associated with developing drugs to specifically treat tinnitus. Consequently, drugs developed for other medical conditions have generally been evaluated to determine whether they can relieve tinnitus. While several double-blind, placebo-controlled, crossover studies have been carried out in tinnitus patients, many reports suffer from the lack of proper experimental controls and small sample sizes. However, advances have been made in the development of animal models in which to test compounds that can suppress noise- or drug-induced tinnitus (51–56). The following sections review many of the drugs used to suppress tinnitus, with a focus primarily on drugs administered systemically rather than locally (57, 58), as oral dosing is most likely to gain widespread acceptance because of convenience, ease of titration and scheduling.

Acamprosate

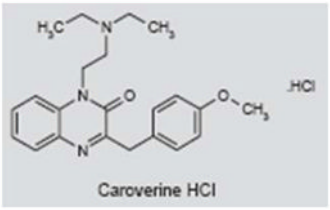


Acamprosate (Campral®) is approved for the treatment of alcoholism in the U.S. and Europe. It presumably blocks excitatory glutamatergic *N*-methyl-d-aspartate (NMDA) receptors (59–61) while enhancing γ-aminobutyric acid (GABA)-mediated nerve inhibition (62–64). However, some studies indicate that acamprosate enhances NMDA function, while others indicate that the compound enhances NMDA-induced excitability at low concentrations and suppresses it at high concentrations (62–65). Other reports suggest that

acamprosate has no effect on GABA-mediated currents (66), and some reports suggest that acamprosate inhibits the binding of taurine to taurine receptors (67).

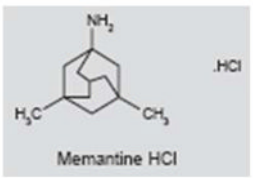
One paper has been published on the use of acamprosate to treat tinnitus patients, most of whom had mild to profound noise-induced hearing loss (68, 69). The rationale for treatment assumes that tinnitus arises from excess glutamatergic activity through NMDA receptors and/or hyperactivity resulting from the loss of GABA-mediated inhibition (70–75). In this double-blind study, patients received placebo or acamprosate (333 mg t.i.d.) and rated the loudness and annoyance of their tinnitus before and at monthly intervals of treatment. Acamprosate had no beneficial effects after 30 days of treatment, a modest benefit at 60 days and a significant effect at 90 days. Approximately 87% of the subjects in the acamprosate group showed some improvement, including three subjects in whom tinnitus disappeared, compared to 44% in the placebo group. A larger clinical trial is currently under way to further assess the encouraging results from this preliminary study (http://clinicaltrials.gov/ct2/show/NCT00596531).

Caroverine



Caroverine (Spasmium-R®) is used as a spasmolytic drug and acts as an antagonist of calcium and non-NMDA and NMDA glutamate receptors (76–80). Because of a limited uptake with oral administration, caroverine is administered intravenously or locally (58, 81). It has been proposed that cochlear synaptic tinnitus arises from a synaptic disturbance of NMDA or non-NMDA receptors on the afferent dendrites of the spiral ganglion neurons (70, 82–84). To test this hypothesis, patients with putative cochlear synaptic tinnitus were enrolled in a single-blind study in which subjects were randomly assigned to a placebo group (i.v. saline) or a caroverine group (a maximum dose of 160 mg i.v.; less if tinnitus reduced or worsened). Tinnitus loudness (5-point scale) and tinnitus matching (intensity and frequency) were measured before and after treatment and at 1 week post-treatment. Significant responders were those that showed a reduction in loudness of 1 point or more and a 50% reduction in intensity (−3 dB). Immediately post-treatment, 63% of the caroverine group and 0% of the placebo group showed a significant response. At 1 week post-treatment, 43% in the caroverine group had a significant positive response compared to 3% in the placebo group. The low positive response rate in the placebo group was unusual, because placebo response rates are typically around 40% (85). While these initial results were encouraging, a subsequent study following the same protocol found no positive effect of caroverine treatment (86).

Memantine

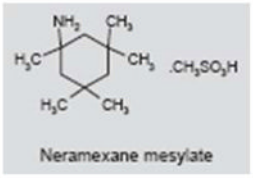


Memantine (Namenda®) is currently used in the treatment of Alzheimer's disease (AD) and has shown positive effects in depression (87, 88). It acts as a voltage-dependent antagonist of NMDA receptors and reduces excitotoxicity by preventing prolonged influx of calcium (89, 90). However, memantine is also known to block serotonin (5-HT) and nicotinic acetylcholine receptors (91, 92). Excitotoxicity mediated by NMDA receptors has been proposed as a mechanism for cochlear tinnitus (70, 82–84). High doses of salicylate, the active ingredient in aspirin, reliably induce tinnitus and augment currents through NMDA receptors on cochlear spiral ganglion neurons (93–95). NMDA antagonists applied locally to the inner ear blocked behavioral evidence of salicylate-induced tinnitus (83). In another behavioral experiment, cochlear application of the selective NMDA antagonist ifenprodil in the first 4 days following noise exposure significantly reduced the probability of developing noise-induced tinnitus (84). In contrast to the positive results seen with cochlear application of NMDA antagonists, systemic memantine administration failed to completely suppress salicylate-induced tinnitus in a behavioral model of tinnitus (51). Likewise, in a prospective, randomized, double-blind, crossover clinical study using the Tinnitus Handicap Inventory to assess efficacy, 90-day treatment with memantine was no more effective than placebo. Moreover, memantine caused side effects in 9% of patients (96).

AM-101

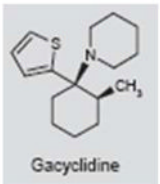
AM-101 is a noncompetitive NMDA antagonist that is being evaluated as a treatment for tinnitus. Based on positive results in animal studies, a double-blind, randomized, placebo-controlled phase IIb trial of intratympanic delivery of AM-101 is currently being carried out. The study involves patients with acute tinnitus (< 3 months) arising from noise trauma or sudden hearing loss who have not responded to glucocorticoid treatment (http://www.aurismedical.com/p/therapies/am_101.php). Patients with acute tinnitus are being enrolled in a clinical trial with AM-101 (http://clinicaltrials.gov/ct2/show/NCT00860808).

Neramexane



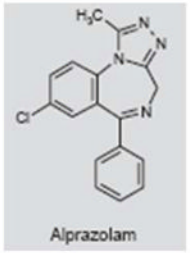
Neramexane, a drug similar to memantine, is being evaluated for AD, drug dependence, depression and pain. Like memantine, neramexane acts as a noncompetitive, voltage-dependent NMDA antagonist. It also blocks α9 and α10 nicotinic cholinergic receptors which are expressed on inner hair cells in the inner ear (97, 98). Developer Merz & Co GmbH is currently conducting a multicenter clinical trial to determine the efficacy of neramexane for treating tinnitus (http://clinicaltrials.gov/ct2/show/NCT00772980).

Gacyclidine



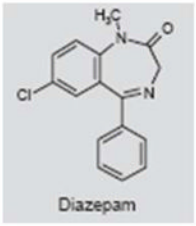
Gacyclidine is another NMDA antagonist under evaluation for the treatment of tinnitus. In animal behavioral studies of salicylate-induced tinnitus, gacyclidine suppressed tinnitus-like behavior when applied bilaterally to the cochlea (83). Nine days of intracochlear perfusion of gacyclidine did not have any adverse effects on the guinea pig auditory evoked responses, suggesting that this treatment may be relatively safe. In preliminary studies in unilateral deaf humans perfusion of gacyclidine on the round window membrane for several days resulted in the temporary relief of tinnitus (99). While the results in the published abstract are encouraging, further work is needed to determine the generality of the findings and if gacyclidine has any long-term benefit.

Alprazolam



Alprazolam (Xanax®) is a short-acting triazolobenzodiazepine used to treat anxiety, panic attacks and depression (100–103). Alprazolam binds to the benzodiazepine site of the $GABA_A$ receptor, where it acts as a GABA agonist by increasing the permeability of chloride ions, leading to hyperpolarization and decreased excitability (104, 105). Complications associated with alprazolam include drug dependency and difficulty of discontinuing use. In a prospective, double-blind, placebo-controlled study, alprazolam was administered to patients with tinnitus (26); the dose was increased until it caused side effects or had an effect on tinnitus. Alprazolam reduced tinnitus loudness, measured with a tinnitus synthesizer and visual analog scale, in 76% of subjects, whereas only 5% showed a reduction in tinnitus loudness in the control group. Although the positive effects of alprazolam observed in this study are encouraging, the study design has been criticized because of the small sample size, drug dosing method, failure to assess emotional effect and the need for replication (49, 106).

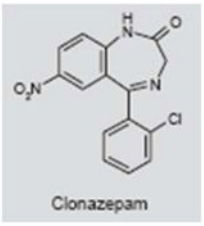
Diazepam



The benzodiazepine diazepam (Valium®) is used to treat anxiety, insomnia, epilepsy, and muscle spasms. It binds to a specific subunit on the $GABA_A$ receptor (107) and is a positive allosteric modulator of GABA that increases hyperpolarization and decreases neuronal excitability. However, diazepam can also bind to voltage-gated sodium channels and reduce excitability by slowing sodium channel inactivation (108). Diazepam was evaluated in a double-blind, triple crossover trial involving 21 tinnitus patients (109). The drug had no effect on tinnitus loudness, a result which is surprising considering that its mechanisms of action are similar to those of alprazolam. One possible explanation for the discrepancy is that the dose of alprazolam, but not diazepam, was adjusted for each patient to maximize its

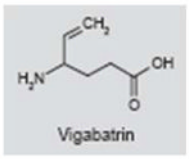
effects on tinnitus (26). Complications associated with diazepam include drug dependency and difficulty of discontinuing use (110, 111).

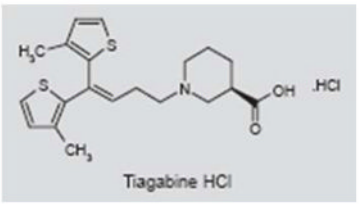
Clonazepam



Clonazepam (Klonopin®) is a benzodiazepine derivative used as a muscle relaxant, anxiolytic and anticonvulsant. Like other benzodiazepines, it binds to specific subunits of the GABA receptor, where it acts as an agonist, leading to hyperpolarization and decreased excitability (107). In a retrospective study of medical records from over 3,000 patients taking clonazepam (0.5–1 mg/day for 60–180 days) for vestibular or cochleovestibular disorders, 32% reported an improvement in their tinnitus (112). The lack of a control group makes it difficult to evaluate the significance of these findings. In a prospective, randomized, single-blind clinical trial involving 10 patients per group, clonazepam significantly reduced tinnitus loudness and annoyance (visual analog scale) relative to the control group (113). Because of the small sample size, lack of double-blind and a crossover design, additional studies are needed to evaluate the efficacy of clonazepam (114). Like other benzodiazepines, drug dependency and difficulty discontinuing use are complicating factors associated with its use in the treatment of tinnitus.

Vigabatrin and tiagabine



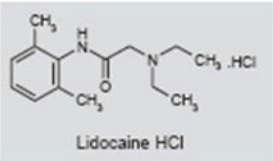


Vigabatrin (Sabril®) and tiagabine (Gabitril®), two drugs that act on different aspects of GABAergic neurotransmission, have been studied in an animal model of noise-induced tinnitus. Vigabatrin is used as an anticonvulsant and to treat infantile spasms. It irreversibly inhibits GABA transaminase (GABA-T), the enzyme that catabolizes GABA, thereby increasing GABA levels (115–117). Vigabatrin also induces tonic release of GABA by causing the GABA transporter to operate in reverse (118). Tiagabine is used to treat seizures and panic disorders (119–121) and acts by inhibiting the uptake of GABA via the GAT-1 transporter, thereby increasing the availability of GABA at its receptor (122, 123).

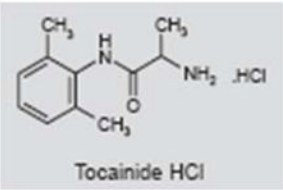
It has been proposed that tinnitus arises from loss of inhibition in the CNS as a result of cochlear deafferentation caused by noise, aging or ototoxic drugs (72, 124–126). To test this hypothesis, noise-exposed rats with behavioral evidence of tinnitus were treated with

vigabatrin or tiagabine. Tiagabine did not suppress noise-induced tinnitus; however, vigabatrin suppressed noise-induced tinnitus, and the tinnitus reappeared when treatment was discontinued (73). We are unaware of any clinical trials in which vigabatrin has been used to treat tinnitus; however, given the positive animal data, vigabatrin is a potential drug candidate for a clinical study in tinnitus. However, it is known that the drug can cause irreversible visual disturbances, limiting it use in humans (127).

Lidocaine



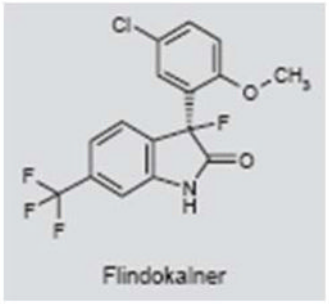
Lidocaine (Xylocaine®) is generally used as a local anesthetic or to treat cardiac arrhythmias (128). It is believed to bind to fast voltage-gated sodium channels, reducing the magnitude of the sodium current during depolarization (129–131). However, the mode of action of lidocaine is more complex, as it is known to affect calcium-, potassium-, and glycine-induced chloride currents at micromolar concentrations (132, 133). In 1935, lidocaine was inadvertently found to suppress tinnitus following nasal administration (134). Since that time, many clinical studies have shown that intravenous lidocaine suppresses tinnitus in a subpopulation of subjects. High positive response rates (~70%) have been reported in some studies, while others have reported lower response rates (~40%), as well as a large percentage of subjects in whom tinnitus became worse (~30%) (135–139). Relatively few patients show large reductions in tinnitus loudness; in those that do, the positive effects tend to be short-lasting (140). The sites of action of intravenous lidocaine are not well understood, but there is evidence that it affects both the cochlea and CNS (139, 141, 142). In one human brain imaging study in which lidocaine either increased or decreased the loudness of tinnitus, the changes in loudness were associated with altered neural activity in the right auditory association cortex (139). Tocainide, an analogue of lidocaine that can be taken orally, was evaluated as a potential long-term therapy for tinnitus. While preliminary results were encouraging, several randomized, controlled studies found that tocainide had little benefit for tinnitus (143–147).



Potassium channel modulators

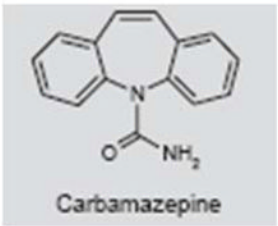
Tinnitus is thought to arise from neural hyperactivity. As potassium ion channels play an important role in regulating the resting potential and spontaneous and evoked neural activity, potassium channel modulators may represent potential therapeutic targets for tinnitus therapy. Potassium channel modulators have also attracted attention as potential therapeutic targets for pain, epilepsy, anxiety and other hyperexcitability disorders (148, 149). In a preliminary report utilizing a rat behavioral model, the potassium channel modulators flindokalner (BMS-204352; MaxiPost™), and its (*R*)-enantiomer (R-MaxiPost™) reduced behavioral evidence of salicylate-induced tinnitus in a dose-dependent manner (150). Both enantiomers are $K_{Ca}1.1$ (BK) positive modulators and $K_v7.1$ negative modulators (149,

151). MaxiPost and its (*R*)-enantiomer modulate $K_v7.2$-$K_v7.5$ ion channels positively and negatively, respectively. These results suggest that potassium channel modulators may represent new therapeutic candidates for tinnitus management.



Carbamazepine

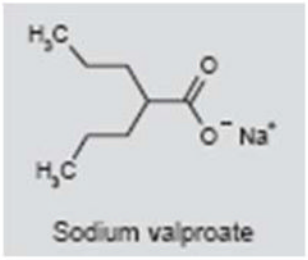
Carbamazepine (Tegretol®) is an anticonvulsant and mood stabilizer used to treat a variety of clinical disorders, including epilepsy, bipolar disorder, schizophrenia, pain and trigeminal neuralgia (152–156). The drug binds to voltage-gated sodium channels and stabilizes the sodium inactivation state, thereby reducing neural firing (157–159). Its mode of action, however, may be more complex than this, as some reports indicate that carbamazepine enhances outward, voltage-dependent potassium currents, inhibits L-type calcium channels and enhances the release of 5-HT (160–162). The results for carbamazepine in the treatment of tinnitus have been mixed. Several randomized clinical trials reported no beneficial effect of carbamazepine on tinnitus (163–165). However, the doses in these studies tended to be low (200 mg/day), and in one study only a single dose was given, which may explain the lack of effect (165). Other reports have shown that, among those patients who responded positively to intravenous lidocaine, 56% had a good or excellent response to carbamazepine (typically administered at 600–1000 mg daily), whereas those that responded poorly to lidocaine also responded poorly to carbamazepine (166). Patients most likely to respond positively to lidocaine were those with cochlear hearing loss. A more recent report found that among positive lidocaine responders, 50% responded positively to carbamazepine (ascending doses of 50–600 mg), carbamazepine had no effect in 29% of lidocaine responders, 15% withdrew because of side effects, and tinnitus worsened in 6% of patients (137). These results suggest that carbamazepine may provide tinnitus relief in roughly half the patients that respond positively to lidocaine.



A rare group of patients who derive significant benefit from carbamazepine are those who have intermittent “typewriter tinnitus”, which is described as sounding like a typewriter, popcorn or ear clicking (44, 45). Radiological analysis showed evidence of vascular compression of the auditory nerve on the same side as the clicking. This suggests that there may be a tinnitus subgroup that can be classified on the basis of tinnitus perceptual characteristics, radiological features and response to drug treatment.

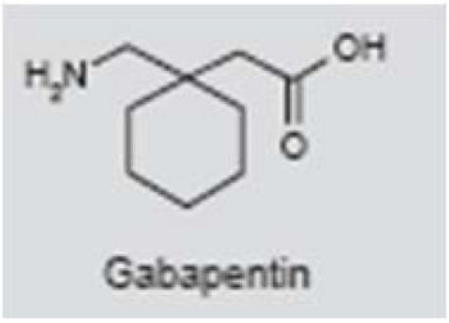
Finally, an animal study evaluated the ability of carbamazepine to suppress salicylate (aspirin)-induced tinnitus in rats. Tinnitus was assessed with a behavioral conditioned, lick-suppression paradigm. Salicylate-induced tinnitus was significantly reduced by 15 mg/kg of carbamazepine, but not by lower or higher doses (167). The neural mechanisms by which carbamazepine suppresses salicylate-induced tinnitus are unclear (83, 126, 167–170).

Sodium valproate/valproic acid



Sodium valproate (Depakene®) is used in the treatment of seizures, bipolar disorders, mood disorders and depression. Valproic acid has a broad spectrum of action that includes inhibition of GABA-T, inhibition of histone and blockade of voltage-gated sodium channels and T-type calcium channels. One case study found that sodium valproate (200 mg b.i.d.) was effective in suppressing tinnitus (171). However, another case study reported that sodium valproate induced tinnitus, and that the tinnitus gradually disappeared when treatment was discontinued (172). Because sodium valproate is sometimes used clinically to treat patients with severe tinnitus (173), well-controlled clinical trials are needed to assess its efficacy.

Gabapentin

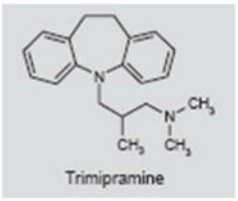


Gabapentin (Neurontin®) is widely used in the treatment of seizures, neuropathic pain and migraine (174–177). Because of its structural similarity to GABA, gabapentin was thought to bind to GABA receptors (178); however, its mechanisms of action are not fully understood. Gabapentin does not act directly on GABA, glycine or glutamatergic receptors, or voltage-gated sodium or calcium channels (179). The drug enhances the stimulated-release of GABA (180), increases GABA levels in patients (181) and, with chronic application, inhibits calcium currents by disrupting calcium channel trafficking (182).

An early case report and several clinical studies suggest that gabapentin may suppress tinnitus (183, 184). In addition, an animal study indicated that gabapentin reversibly suppressed behavioral evidence of noise-induced tinnitus in rats (185). Despite these positive findings, several large, randomized clinical trials found that gabapentin was not significantly different from placebo in treating tinnitus, with the possible exception that it reduced tinnitus annoyance in a subgroup of patients with noise-induced tinnitus (186–189).

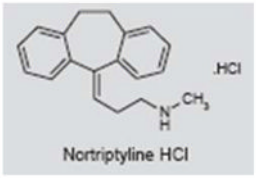
The overall trend that has emerged from randomized clinical trials is that gabapentin may be of limited value in treating tinnitus.

Trimipramine



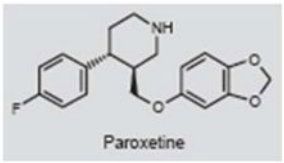
Trimipramine (Stangyl®) is classified as a tricyclic antidepressant; however, its mode of action differs from other tricyclic antidepressants in that it is a weak to moderate inhibitor of norepinephrine and 5-HT. However, trimipramine also blocks some dopamine and 5-HT receptors and alters the concentration of dopamine and 5-HT (190, 191). Trimipramine was evaluated in a double-blind, placebo-controlled, crossover study (192). Of the 19 subjects completing the study, 47% reported improvement and 37% claimed worsening of their tinnitus with trimipramine, whereas 42% reported improvement and 21% reported worsening with placebo. These results suggest that trimipramine has little or no benefit in the treatment of tinnitus.

Nortriptyline



Nortriptyline (Aventyl®) is tricyclic antidepressant that is also used to treat chronic fatigue, migraine and chronic pain (193–196). Its primary mode of action is to inhibit the reuptake of norepinephrine and, to a lesser extent, 5-HT. Nortriptyline also blocks muscarinic and 5-HT receptors. In a small, single-blind, placebo-washout study involving patients with severe tinnitus and major depression, nortriptyline significantly reduced depression and tinnitus loudness (10-dB reduction) (197). In a double-blind, placebo-controlled, follow-up study involving subjects with severe tinnitus and severe depression or depressive symptoms, nortriptyline significantly reduced depression scores, tinnitus disability scores and tinnitus loudness (6.4-dB reduction) relative to placebo (198). There was a significant correlation between the reduction in tinnitus disability scores and depression scores (199). These results suggest that nortriptyline is effective in reducing tinnitus loudness and severity in severely depressed tinnitus patients, but has less benefit in nondepressed individuals.

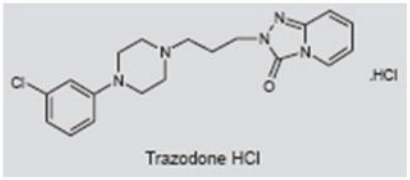
Paroxetine



Paroxetine (Paxil®) is an antidepressant that is also used to treat post-traumatic distress disorder, obsessive-compulsive disorder, anxiety and panic disorder (200–202). Paroxetine

is a potent and highly selective serotonin reuptake inhibitor (SSRI) and shows weak binding to muscarinic acetylcholine receptors (203, 204). In a double-blind, placebo-controlled study involving chronic tinnitus patients, few of whom suffered from depression, the paroxetine group showed little difference from placebo on tinnitus loudness matching, Tinnitus Handicap Questionnaire scores and other measures; however the paroxetine group showed a significant improvement in tinnitus aggravation compared with the control group (205). Although SSRIs are widely used to treat tinnitus (206), the authors suggested that antidepressants should not be used to treat nondepressed tinnitus patients. However, in a case study, paroxetine significantly reduced tinnitus and improved mood in a patient with severe depression, anxiety and tinnitus (206).

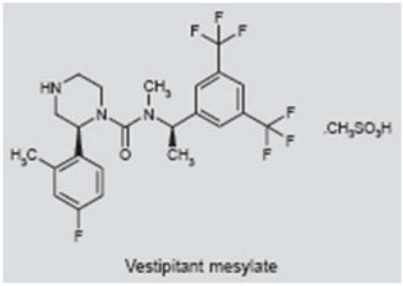
Trazodone



Trazodone HCl

Trazodone (Desyrel®) is an antidepressant with a dual mode of action: it is an SSRI and also selectively blocks postsynaptic 5-HT_{2A} and 5-HT_{2C} receptors. In addition to its use as an antidepressant, trazodone is also used to treat insomnia. It main side effects are drowsiness and hypotension. Trazodone was evaluated in a prospective, placebo-controlled, double-blind trial involving 83 subjects - approximately half each in the placebo and treatment groups. Subjects were treated with trazodone for 60 days at 50 mg/day. Patients in both the placebo and trazodone arms showed significant improvement in tinnitus loudness, discomfort and quality of life; however, the differences between the placebo and trazodone groups were not statistically significant. Thus, trazodone was not shown to be effective in treating tinnitus using this particular regimen and in this patient population.

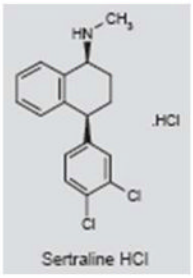
Vestipitant/paroxetine combination therapy



Vestipitant mesylate

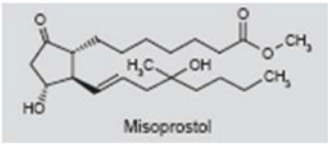
Vestipitant and the combination of vestipitant and paroxetine are currently undergoing a phase II clinical trial for the treatment of tinnitus (http://clinicaltrials.gov/ct2/show/NCT00394056); information on the clinical efficacy of these drugs is currently unavailable. Vestipitant is a novel antagonist of the tachykinin NK_1 receptor that binds substance P. Substance P acts as a neurotransmitter and neuromodulator. NK_1 receptor antagonists suppress pain (207, 208). Neurokinin receptors are present in the inner ear and therefore represent a potential therapeutic target for tinnitus (209, 210). Paroxetine is an SSRI used to treat depression, obsessive-compulsive disorder and anxiety (211).

Sertraline



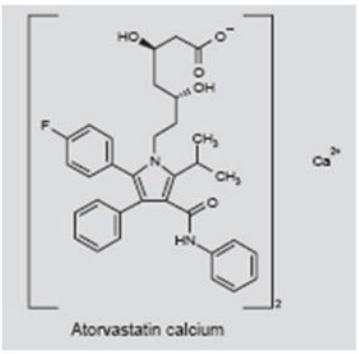
Sertraline (Zoloft®) is used to treat major depression, anxiety, obsessive-compulsive behavior and panic disorder (212–214). It mainly acts as an SSRI by suppressing the serotonin transporter (215); however, it also inhibits the dopamine transporter and the σ_1 receptor (216). In a randomized, double-blind, placebo-controlled study in patients without severe hearing loss but with depression, anxiety and a high risk for developing severe tinnitus, sertraline was shown to be significantly more effective than placebo in reducing tinnitus loudness (12 dB versus 4 dB) and tinnitus severity (4.7 versus 2.7), but not tinnitus annoyance. Collectively, the results suggest that tinnitus patients with depression and anxiety may gain some benefit from antidepressant treatments (217).

Misoprostol



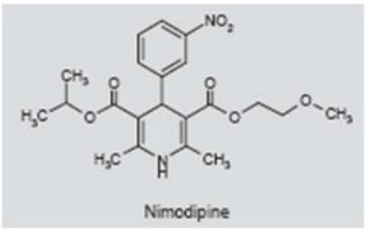
Misoprostol (Cytotec®) is a synthetic prostaglandin E_1 (PGE_1) analogue (218) that is primarily used to prevent gastric ulcers induced by non-steroidal anti-inflammatory drugs such as aspirin and to induce labor (219–221). It also inhibits the release of inflammatory cytokines (222). In a small, placebo-controlled, semi-crossover study, tinnitus was improved (reduced severity, improved sleep and concentration) in 33% of subjects during misoprostol treatment (escalating to 800 μg/day), whereas no subjects improved in the placebo group (223). In a subsequent double-blind, placebo-controlled study, the proportion of subjects showing a > 15-dB reduction in tinnitus loudness was significantly greater in the misoprostol group (800 μg/day) than in the placebo group. Surprisingly, misoprostol did not show significant benefit on other tinnitus measures. In a third randomized, controlled study involving tinnitus patients with hypertension and/or diabetes, the decrease in tinnitus loudness was significantly greater in the misoprostol group (46% of patients) than the placebo group (14% of patients); surprisingly, the subjective measures of tinnitus were not different (224). Overall, the studies suggest that misoprostol may provide some benefit to tinnitus patients with minimal risk, but larger studies are needed to confirm these trends before misoprostol can be considered of significant benefit for tinnitus.

Atorvastatin



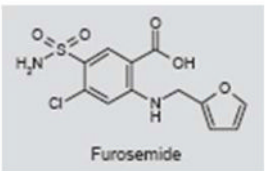
The statin atorvastatin (Lipitor®) is used extensively to lower blood cholesterol and prevent strokes (225, 226). The drug inhibits HMG-CoA reductase, which suppresses the production of mevalonate, in turn reducing the synthesis of cholesterol (227). Atorvastatin also improves circulation and reduces inflammation and oxidative stress (228, 229). In a 13-month, randomized, double-blind, placebo-controlled study involving elderly patients with elevated cholesterol, atorvastatin failed to slow the progression of age-related hearing loss and did not significantly reduce tinnitus, although there was a trend toward a beneficial effect that did not reach significance (230).

Nimodipine



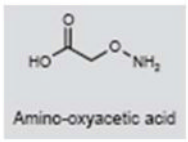
The L-type calcium channel blocker nimodipine (Nomotop®) was originally used for the treatment of high blood pressure, but is now primarily used in the treatment of subarachnoid hemorrhage (231, 232, 233). Nimodipine crosses the blood-brain barrier, dilates cerebral blood vessels and improves cerebral blood flow. The first open-label clinical trial found that nimodipine had positive effects on tinnitus in many patients, but the lack of a placebo control made it difficult to gauge its efficacy (234). Subsequent behavioral studies in rats showed that nimodipine significantly reduced tinnitus-like behavior caused by high doses of quinine or sodium salicylate (54, 235, 236). However, a second open-label clinical trial found significant improvement in the subject rating of tinnitus in only 5 of 31 (16%) patients; 17 patients (55%) showed no change and 6 patients (19%) showed marginal to major worsening of their tinnitus (237). Because there were few positive responders, it was concluded that a large-scale, randomized, placebo-controlled study was not warranted.

Furosemide



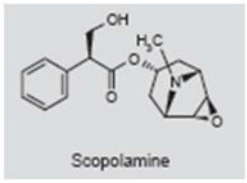
Furosemide (Lasix®) is a loop-inhibiting diuretic used to treat congestive heart failure and edema (238). It inhibits the Na-K-2Cl cotransporter that transports sodium, potassium and chloride ions into and out of cells (239). The Na-K-2Cl cotransporter is expressed in the inner ear, as well as in the brain (240, 241). Furosemide also blocks $GABA_A$ receptors (242). The drug has been proposed as a treatment for tinnitus of cochlear origin because it strongly suppresses the endolymphatic potential and other cochlear responses (243). It has been reported that ~50% of patients note a reduction in tinnitus symptoms following intravenous furosemide treatment; these positive responders were hypothesized to have cochlear tinnitus, whereas those who did not respond were assumed to have central tinnitus. In contrast, patients with presumably central tinnitus (i.e., tinnitus emanating from a surgically ablated ear) did not show a reduction in their tinnitus (244). Furosemide has also been found to suppress tinnitus in ~40% of patients with Meniere's disease (245). However, high doses of furosemide can also induce temporary hearing loss and tinnitus (246–248). Thus, the data on the use of furosemide to treat tinnitus and conclusions regarding its central versus cochlear mode of action are difficult to interpret, especially when considering that Na-K-2Cl transporters are present in both the ear and brain.

Amino-oxyacetic acid



Amino-oxyacetic acid (AOAA) is an anticonvulsant that potently inhibits GABA-T, leading to the buildup of GABA in the brain, thereby strengthening its inhibitory effects (249, 250). AOAA also reduces the endocochlear potential in the cochlea (251). Because of its cochlear effects, AOAA was evaluated as a treatment for tinnitus presumably of cochlear origin (252). AOAA reduced tinnitus severity in ~20% of patients; however, > 70% of patients experienced severe side effects, thereby ruling out the clinical utility of this compound (253).

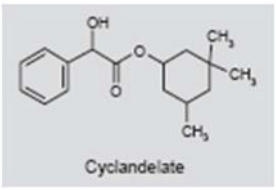
Scopolamine



Scopolamine is used to treat motion sickness, nausea and intestinal cramps (254, 255). It acts as a competitive antagonist of M_1 muscarinic acetylcholine receptors, which are widely distributed in the brain and along the auditory pathway (256–259). A literature search failed to turn up any clinical report in which scopolamine has been used to treat tinnitus. One animal study, however, suggested that scopolamine might be effective in suppressing salicylate-induced tinnitus (93, 94). The rationale for using scopolamine is based on the fact that high doses of salicylate significantly increase the expression of the activity and plasticity-related proteins c-fos and arg3.1 in the auditory cortex and amygdala; these proteins were considered putative markers of tinnitus-related neural activity (260). The amygdala sends axons to the nucleus basalis, which in turn sends cholinergic fibers to the auditory cortex, and scopolamine was proposed as a treatment for salicylate-induced tinnitus as it suppresses the expression of c-fos and arg3.1 in the auditory cortex. However, when behavioral measures of tinnitus were obtained from rats treated with salicylate or salicylate

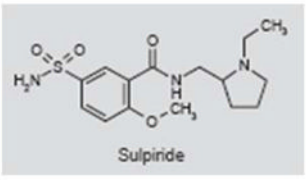
plus scopolamine, scopolamine failed to suppress salicylate-induced tinnitus (261). On the basis of these results, it seems unlikely that scopolamine will be effective in treating tinnitus.

Cyclandelate



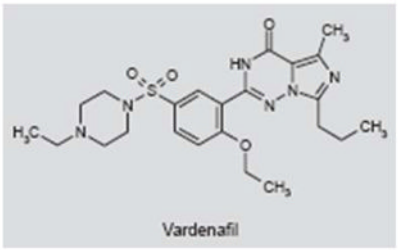
Cyclandelate is a vasodilator that is believed to act by blocking the influx of calcium into cells (262, 263). It is mainly used to treat peripheral vascular disorders, but is sometimes used to treat cerebrovascular disorders (264). Because some reports suggest that tinnitus arises from vascular insufficiency affecting the labyrinthine or brain (265, 266), cyclandelate was investigated as a treatment for tinnitus. In an open-label, nonrandomized, multicenter clinical trial in patients with tinnitus, vertigo and visual disturbances, 90 days of treatment with cyclandelate reportedly reduced the severity and frequency of these symptoms, with minimal side effects (267). However, in a subsequent placebo-controlled, double-blind study, cyclandelate did not significantly change audiometric measures of tinnitus loudness and pitch. The number of positive tinnitus responders was small and not significantly different from the placebo group, and many patients reported side effects (268). Thus, there is no clear evidence that vasodilators such as cyclandelate improve tinnitus symptoms.

Sulpiride



Sulpiride (Meresa®) is an antipsychotic drug that selectively blocks dopamine D_2 receptors (269, 270). Several studies have explored the use of sulpiride to treat tinnitus based on models and data suggesting that dopaminergic pathways in limbic, prefrontal and temporal areas of the cortex contribute to tinnitus severity (271–274). In one double-blind, placebo-controlled study, sulpiride significantly reduced subjective ratings of tinnitus and tinnitus visual analog scale scores; the reductions with sulpiride were not significantly greater than those produced by placebo. However, the combination of sulpiride plus melatonin, which interacts with dopamine receptors, reduced tinnitus visual analog scale scores significantly more than placebo (275–277). In a single-blind, placebo-controlled study, sulpiride plus hydroxyzine, an antihistamine and anxiolytic, was significantly more effective in reducing tinnitus visual analog scale and tinnitus perception scores than placebo or sulpiride alone (278). These preliminary studies suggest that D_2 antagonists such as sulpiride may help to suppress tinnitus symptoms, but further work is needed to confirm or refute these findings.

Vardenafil



The phosphodiesterase type 5 (PDE5) inhibitor vardenafil (Levitra®) prevents the degradation of cyclic GMP found in the vascular smooth muscles of the penis and lungs (279). Vardenafil is primarily used to treat male impotence and sometimes pulmonary hypertension (280). While vardenafil is generally well tolerated, common side effects include headache, flushing, nasal congestion and dyspepsia (281). In a recent clinical report, the rationale for evaluating the effects of vardenafil on tinnitus was based on informal patient reports claiming that their tinnitus improved significantly when taking vardenafil (282). The efficacy of vardenafil was evaluated in a randomized, double-blind, placebo-controlled study with 21 patients receiving placebo or vardenafil (10 mg b.i.d. for 12 weeks). The major outcome variables relevant to tinnitus (Tinnitus Questionnaire, tinnitus loudness or pitch and other audiometric measure) failed to reveal any clinical or statistically significant improvement. Therefore, vardenafil does not appear to be a suitable treatment for tinnitus.

Ginkgo biloba

Extracts derived from the ancient Chinese *Ginkgo biloba* tree yield EGb-761, the active component, which contains bioactive flavonoids, terpenes and vasoactive compounds. Because of its vasodilating and antioxidant properties, *Ginkgo* has been used to treat a wide range of disorders, including tinnitus (283). Several studies have reported that *Ginkgo* alleviates tinnitus symptoms, particularly in patients with short-duration symptoms (265, 284). In addition, one behavioral study with rats found that EGb-761 reduced the behavioral manifestations of salicylate-induced tinnitus (285). However, a growing body of evidence from large, well-controlled, double-blind, placebo-controlled clinical studies clearly indicates that *Ginkgo* is no more effective in alleviating tinnitus symptoms than placebo (286–291).

Melatonin

Melatonin, a naturally occurring circulating hormone produced in the pineal gland and other tissues, binds to melatonin receptors and plays an important role in regulating circadian rhythms (292, 293). Melatonin is also a potent antioxidant that protects mitochondrial and nuclear DNA (294, 295) and has been found to protect against noise- and drug-induced hearing loss (296, 297). Because sleep disturbances represent a major complaint and complicating factor in tinnitus, melatonin was evaluated as a treatment for tinnitus in three studies. In the first double-blind, placebo-controlled, crossover study, scores of tinnitus severity measured with the Tinnitus Handicap Inventory improved by approximately the same degree with melatonin and placebo. There was a trend toward improved sleep scores with melatonin, but the effect was not statistically significant (298). A subsequent open-label study found statistically significant improvements on the Tinnitus Handicap Inventory and Pittsburgh Sleep Quality Index with melatonin treatment; however, it is difficult to evaluate the significance of these findings because of the lack of a placebo control group and moderate effect size (299). A more recent, randomized, double-blind, placebo-controlled study found that melatonin reduced subjective ratings of tinnitus and tinnitus loudness more

than placebo; these improvements were substantially larger if melatonin was combined with the antipsychotic sulpiride, a selective dopamine D_2 antagonist (275).

Zinc supplements

Zinc, an essential trace metal that plays an important role in numerous biological functions, is widely expressed in the auditory pathway, including the dorsal cochlear nucleus, a structure posited to be a major tinnitus generator (300–303). Zinc has been proposed as a treatment for tinnitus, particularly in patients with hypozincemia (304–307). While positive results have been reported in some patients (308), most well-controlled, double-blind, placebo-controlled studies have found little or no improvement in tinnitus with zinc therapy, except in a few patients with low zinc serum levels (290, 309, 310). A clinical trial to evaluate the efficacy of a dietary zinc supplement for treating tinnitus is under way (http://clinicaltrials.gov/ct2/show/NCT00683644).

SUMMARY AND OUTLOOK

The neural mechanisms that give rise to tinnitus are likely to be just as complex and multifaceted as other neurological disorders, such as epilepsy, pain or depression. The lack of a clinically relevant, objective and valid framework for classifying and distinguishing patients who present with tinnitus symptoms represents a major challenge for clinicians. Efforts are currently under way to develop more clinically relevant schemes for classifying tinnitus patients based on etiology, somatic, audiometric, perceptual and psychological features, as well as brain imaging findings (41, 272, 311–316). Advances in classifying tinnitus patients are likely to lead to improved success rates with drugs targeted to specific subpopulations.

For many years, the standard of care for dealing with tinnitus patients has been, “You need to learn to live with it.” Over the past two decades, a small cadre of clinicians has significantly advanced the standard of care by providing patients with sound therapy, counseling and education (24, 317–319). While many tinnitus patients demonstrate slow, steady improvement with these methods, most patients would prefer a drug therapy that would rapidly lead to improvement and complete suppression of their tinnitus. Aside from a few exceptional cases, most currently available drugs fail to completely suppress tinnitus, although some drugs have been reported to provide moderate relief of symptoms in a subset of patients. Careful clinical observations, along with data from clinical trials, have provided useful clues for deciding on a rational course of drug therapy for select patients. A rare subgroup of patients who describe their tinnitus as sounding like a typewriter is likely to gain significant tinnitus relief from carbamazepine (44, 45). For other patients, carbamazepine is likely to be no better than placebo. When a shotgun approach is used to treat all tinnitus patients with antidepressants, the overall success rates have proved disappointing (205, 206). However, if tinnitus patients with severe depression are treated with antidepressants, tinnitus symptoms often show noticeable improvement (197, 206, 217). Administering a depression inventory to all patients seeking treatment would help identify those patients likely to obtain tinnitus relief from antidepressant therapy (199, 320). Not surprisingly, patients with roaring tinnitus often find it difficult to fall asleep. Sleep deprivation adds to the fatigue, emotional burden and stress associated with tinnitus. Melatonin, an over-the-counter sleep aid with antioxidant properties and minimal side effects, may prove helpful in reducing tinnitus symptoms in patients with significant sleep disturbances. Preliminary studies combining melatonin with the dopamine D_2 antagonist and antipsychotic sulpiride have yielded promising results, but further work is need to confirm these findings (275–277).

Because little is known about the underlying neural mechanisms that cause tinnitus, the clinical approaches to implementing drug therapies for treating tinnitus have been largely hit or miss. The development of behavioral measures of tinnitus in animals, combined with physiological, biochemical, molecular and imaging techniques are likely to provide important insights on the underlying causes of tinnitus (51, 54, 73, 321). Behavioral methods for detecting tinnitus in animals will allow new or existing drugs to be screened to determine if they can suppress tinnitus. The studies carried out to date suggest that GABA-T inhibitors and potassium channel modulators are potential drug candidates for tinnitus (73, 150).

The potential market for an FDA-approved drug to treat tinnitus is quite large; however, the acceptance by the medical community of new or old drugs to treat tinnitus ultimately rests on significant positive findings from well-controlled, multicenter clinical trials. Several existing drugs have been reported to provide significant relief from tinnitus; however, many of these studies suffer from small sample size, lack of replication, unusual dosing methods or weak experimental design, thereby hindering the acceptance of these drugs by the medical community (26, 106, 223, 224). Looking to the future, patients and clinicians may finally receive clear-cut answers from clinical trials currently under way to evaluate the efficacy of neramexane, vestipitant alone and in combination with paroxetine, acamprosate, AM-101 and dietary zinc supplements. Information gleaned from ongoing and future clinical studies may have the potential to revolutionize the treatment of tinnitus.

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