

What's the Buzz?

Treatment Strategies in Chronic Subjective Tinnitus

Tinnitus can be a debilitating condition that affects quality of life and is often not treated according to guidelines. Cognitive behavioral therapy and tinnitus retraining therapy have been successful in reducing tinnitus bother; pharmacotherapy is not widely accepted as successful, and can, in fact, be deleterious. This article describes pathophysiologic disturbances of hearing and how they relate to chronic subjective tinnitus, discusses the clinical evaluation of tinnitus as a presenting symptom, and reviews current treatments.

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The authors have no financial relationships to disclose.

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LEARNING OBJECTIVES

- Distinguish primary tinnitus from secondary tinnitus.
- Understand and implement a full clinical evaluation of tinnitus, including imaging studies when appropriate.
- Discuss expectations regarding treatment options and realistic outcomes of currently recommended therapy.
- Direct patients to specialist care for cognitive behavioral therapy or tinnitus retraining therapy.
- Know when pharmacotherapeutic intervention is indicated.



Primarily chronic subjective tinnitus, often thought of more as a symptom than a diagnosis, affects millions of people worldwide. This troublesome condition has been chronicled as far back as the first century AD, when Celsus gave detailed accounts in his treatise, *De Medicina*.¹

It is estimated that only 20% of people who experience tinnitus actively seek treatment.² In the United States, 2 to 3 million of the 12 million patients who do request treatment report lasting symptoms that they describe as debilitating.³ For patients who seek help, the treatment recommended by physicians is typically pharmacotherapeutic—which does not follow guidelines.⁴

The aim of this article is to reinforce a greater understanding of the mechanisms of tinnitus and integrate that knowledge into treatment guidelines. The article does *not* discuss surgical treatment of tinnitus.

DEFINITION AND CLASSIFICATION

A universal standard definition of chronic tinnitus does not exist; Trevis et al define it as a phantom sound that persists for more than three months.⁵ The quality and loudness of tinnitus is variable but is often described as a buzz, hiss, or ringing. Prevalence increases with age, smoking, male gender, and ethnicity, with the non-Latino white popula-

tion statistically at greater risk.³ Comorbid conditions (eg, diabetes and other autoimmune diseases) are risk factors for tinnitus. A history of exposure to loud sound—occupational, environmental, or recreational—also can predispose a person to tinnitus.³

The American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) classifies tinnitus as primary (subjective) or secondary (objective). Primary tinnitus—representing the majority of cases—has no identifiable cause; there may be accompanying sensorineural hearing loss or hyperacusis. Secondary tinnitus can also be associated with sensorineural hearing loss but has an identifiable underlying cause.⁶ The differential diagnosis of tinnitus is listed in the Table (see next page).⁷

Tinnitus is further defined by its persistence. *Persistent tinnitus* is defined as tinnitus lasting more than six months, slightly longer than the duration offered by Trevis et al, who also define tinnitus as *bothersome* or *non-bothersome*, depending on its impact on quality of life.^{5,6} Causes of reduced quality of life include depression, anxiety, insomnia, and neurocognitive decline—all of which have been associated with chronic subjective tinnitus.⁸

Researchers have discovered that tinnitus is not simply a cochlear phenomenon. The pathology extends well beyond the auditory complex, having a deleterious effect on both the somatosensory and central nervous systems, providing some explanation for the prevalence of anxiety and depression associated with the disorder (see "Pathophysiology of tinnitus," page 34).^{9–17}

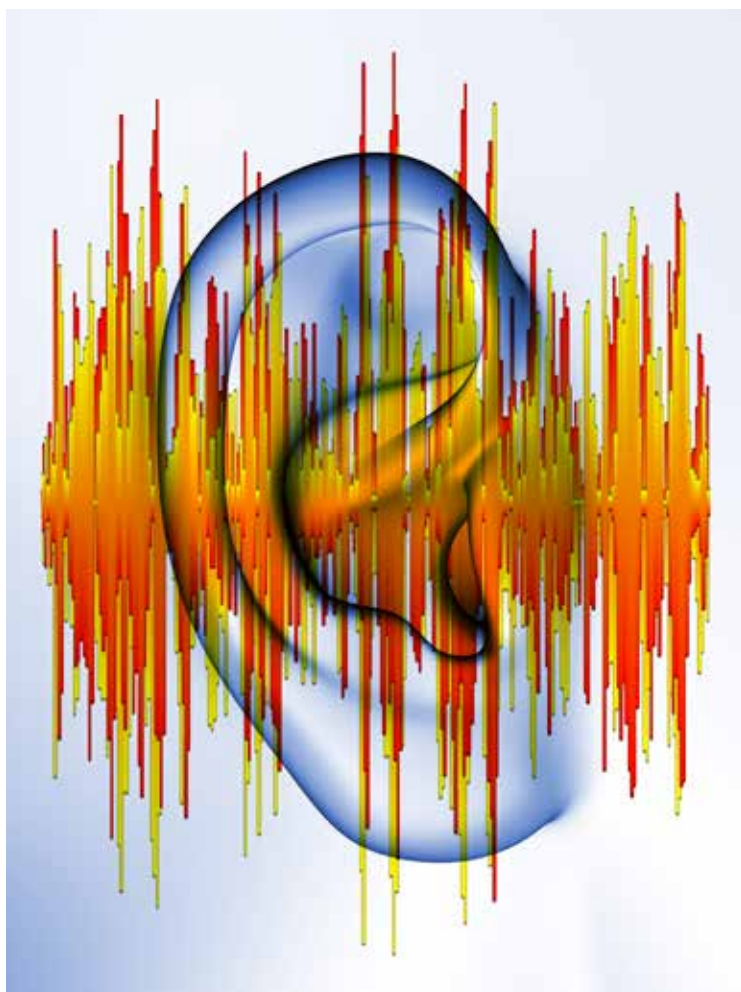
Because of the insidious nature of tinnitus and lack of standard measures of severity, true prevalence is difficult to calculate.¹⁸

CLINICAL EVALUATION

Tinnitus can be a presenting complaint or elicited during history-taking. Symptomatic patients should receive full evaluation, including a complete physical exam, medication history, and laboratory workup.

Adverse effect of drugs

Medications that commonly cause tinnitus symptoms are NSAIDs, chemotherapeu-



tic agents, and antibiotics (eg, macrolides and fluoroquinolones). Amiodarone, ACE inhibitors, proton-pump inhibitors, and calcium-channel blockers have also been implicated. Paradoxically, anxiolytics and tricyclic antidepressants, which are sometimes used to treat tinnitus, have been linked to causing the condition.⁷

Laboratory tests and imaging

Testing should include investigation for infectious disease, autoimmune disorders, and vitamin deficiency.⁷ According to the American College of Radiology, imaging is unnecessary in the workup of primary tinnitus. Any suspicion of a vascular cause noted on the physical exam (eg, an associated bruit or venous hum), however, should be explored with imaging. Furthermore, any case of tinnitus that lateralizes also requires additional investigation. Modalities of choice are MRI, CT, and CT angiography.¹⁹

Referral for audiology evaluation

When no underlying pathology can be identified for tinnitus, the patient should be sent

TABLE
Differential Diagnosis of Tinnitus

Ear disturbances	Oncologic and tumors
Inner ear Mènière disease Otitis media Otosclerosis Perilymph fistula Superior canal dehiscence Vestibular neuritis	Astrocytoma Glioma Paraganglioma Vascular tumor Vestibular schwannoma
Outer ear Cerumen impaction Cholesteatoma Eustachian tube dysfunction Temporomandibular joint dysfunction	Vascular Aberrant carotid artery Arteriovenous malformation Coronary artery disease Intracranial hypertension Microvascular compression Venous hum
Medications	Other causes
ACE inhibitors Antibiotics Antidepressants Antimalarial agents Anxiolytics Caffeine Calcium-channel blockers Chemotherapeutic agents Diuretics NSAIDs Proton-pump inhibitors	Age-related hearing loss (presbycusis) Alcohol Autoimmune disease Gender Idiopathic Lead poisoning Lyme disease Noise-induced Smoking Syphilis Trauma Vitamin deficiency (various)

Source: Adapted from Dinces.⁷

for a full audiology evaluation to screen for associated hearing loss. Discussion of audiology screening tests is beyond the scope of this article; however, testing includes otoscopy, audiography, tympanography, otoacoustic emission testing, auditory brainstem-response testing, and vestibular evoked myogenic potential testing.⁷

Probing nonphysical impacts

Quality of life and overall emotional wellness, including cognitive function, should be investigated in patients with tinnitus. Two questionnaires commonly used in the

assessment of *tinnitus bother* are the Tinnitus Handicap Inventory and the Tinnitus Reaction Questionnaire.⁷ In a large, systematic review, Trevis et al report that “64% of studies investigating depression found an increase in depressive symptoms in people with chronic tinnitus compared to hearing control groups, and 62% of studies investigating anxiety reported significantly increased anxiety symptoms.”⁵

MANAGEMENT

Tinnitus management should be viewed two ways: treatment of perceived loudness and treatment of comorbid symptoms relating to tinnitus bother.⁶ In the same meta-analysis, Trevis and colleagues found that patients with tinnitus had higher rates of anxiety, depression, and overall decline in cognitive function, including processing speed, concentration, and sleep disorders.⁵ It is useful to keep this observation in mind when reviewing treatment options for tinnitus.

Five classic pharmacotherapeutic approaches to tinnitus management are

- Anticonvulsants
- Antidepressants
- Anesthetics
- Anxiolytics
- Lidocaine.

Newer medications that show some promise are N-methyl-D-aspartate (NMDA) receptor antagonists, notably neramexane. Alternative pharmaceuticals include vitamin-based treatments, cannabinoids, and herbal compounds.

The AAO-HNS supports nonpharmacotherapeutic treatment of tinnitus; its guidelines include a recommendation for cognitive behavioral therapy (CBT) as primary therapy.⁶ In addition, tinnitus-retraining therapy, tinnitus-masking therapy/sound therapy, meditation/mindfulness, and yoga all have been studied for their ability to alleviate tinnitus bother.

Pharmacotherapeutic management

Anticonvulsants have failed to provide strong evidence of usefulness in the treatment of tinnitus and are not supported by the AAO-HNS as such.⁶ This conclusion notwithstanding, the anticonvulsants carbamazepine and gabapentin have historically been two of the more common medications used to treat tinnitus.

Carbamazepine is a glutamate receptor antagonist that suppresses seizure activity. Based on prior research suggesting that spontaneous firing within the auditory complex is similar to seizure activity, Iranian researchers explored the hypothesis that carbamazepine might lessen tinnitus severity. Their study revealed, however, that carbamazepine did not statistically significantly reduce the severity of tinnitus, compared to placebo.²⁰ While carbamazepine may be of limited use in the treatment of subjective tinnitus, recent literature confirms that it is not only useful, but also diagnostic, in *typewriter tinnitus* (ie, having a staccato quality, like the sound of typewriter keys being depressed). Typewriter tinnitus is a secondary cause of tinnitus related to disruption of the stapes in the middle ear.²¹

Gabapentin works by promoting gamma-aminobutyric acid (GABA) production in the brain. GABA is an inhibitory neurotransmitter, thus slowing down signals between neurons. Following on preliminary research that detected low levels of GABA in the inferior colliculus of rodents with salicylate-induced tinnitus, Aazh and colleagues conducted a double-blind study of gabapentin—and concluded that it yielded no improvement in symptoms, compared to placebo.²²

Valproic acid has not been formally investigated but is commonly incorporated in the treatment of tinnitus.²³ Lamotrigine has provided similarly disappointing results in the treatment of tinnitus.²⁴

Antidepressants and anxiolytics. Based on the results of their early clinical trials, Sullivan and colleagues concluded that tricyclic antidepressants produced significant improvement in tinnitus symptoms, due to the analgesic effects of these drugs. The re-

searchers studied nortriptyline specifically; in severely depressed patients, the drug reduced the loudness of tinnitus and depressive symptoms. In non-depressed subjects, however, nortriptyline was not as efficacious.²⁵

Selective serotonin reuptake inhibitors have not had the same success as nortriptyline. In a study of paroxetine conducted by Oishi and colleagues, there was little evidence that the drug reduced the loudness of tinnitus, although overall, it did reduce tinnitus bother and anxiety.²⁶

Included in the category of anxiolytics, benzodiazepines have long been used to treat severe tinnitus-induced anxiety, with some success. However, as Elgoyhen and Langguth point out, studies of benzodiazepines for tinnitus have been limited in size.²³

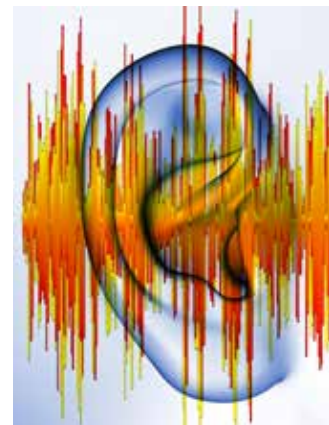
The AAO-HNS does not support routine use of antidepressants and anxiolytics for tinnitus bother.⁷

NMDA receptor antagonists. In a recent clinical trial, neramexane was studied for its efficacy in tinnitus. Neramexane acts at the cholinergic nicotinic and NMDA receptors in the efferent auditory system. Its complex reaction is thought to prevent transmission of unwanted sound not only to structures within the auditory system but beyond, to the medial geniculate body and lateral nucleus of the amygdala. The trial has proved some benefit concerning overall perception of tinnitus loudness; a phase 2 trial is being conducted.²⁷

Intra-tympanic anesthetics. Anesthetics, such as lidocaine, have had limited success and results have not been found to be sustained.

Alternative medical managements

Traditional Chinese herbal medications have been used for centuries and are increasingly popular in Western culture. Hilton and colleagues studied *Ginkgo biloba*, or maidenhair tree, a traditional Chinese herbal supplement available as an extract and as dried leaves. The main action of the extract is vasoregulatory; antiplatelet effects are also seen. Adverse effects include



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Pathophysiology of Tinnitus

Hearing begins as an impulse generated by a literal wave of endolymph as it moves across the basement membrane within the organ of Corti, causing the stereocilia in the inner and outer hair cells to move. Action potentials generated by this movement cause a flow of ions that rush through the membranes of hair cells and summate in the spiral ganglion. These impulses travel the course of the auditory nerve and enter the cranium, reaching the cochlear nuclei in the medulla oblongata of the brainstem.

Pujol and colleagues explain that these fibers are well organized and form a perfectly orchestrated tonotopic map as they are met by specific neurons in the cochlear nuclei. These neurons decode the intensity, and decipher the start and end, of each sound.¹⁰

Each nerve fiber splits into a “V” shape, with one ventral and one dorsal attachment within the cochlear nuclei. The signals travel to the superior olivary complex of the medulla oblongata, the lateral lemniscus, and the inferior colliculus, then spiral upward to the medial geniculate body before entering the auditory cortex in the central nervous

system for final decoding and response.¹⁰ In addition to impulses traveling within the primary auditory complex, the nonauditory complex and somatosensory areas of the brain also receive input.¹¹

Any disruption of the auditory pathway can distort sound; however, recent clinical research is focusing less on the damaged stereocilia and more on the effect that damaged cells have on central auditory pathways.¹² That is to say: Although damage to the inner and outer hair cells remains an important factor in triggering tinnitus, such damage does not explain why people with similar hearing loss, or no loss, can differ so drastically in suffering from tinnitus.¹³

Within the primary auditory complex, the dorsal cochlear nuclei demonstrate the most significant disruption due to damaged stereocilia.¹² Kaltenbach reported that these cells exhibit an increase in the spontaneous firing rate in response to lost frequencies, which are then relayed to higher cortical structures outside the primary auditory complex.¹⁴ Feedback loops between these neurons in the limbic and paralimbic structures usually prevent the signal

gastrointestinal upset and headache. In a systematic review, Hilton and colleagues concluded that *Ginkgo* did not reduce overall tinnitus loudness or severity; the review was limited, however, by the fact that only two studies met criteria for inclusion.²⁸

Vitamins, lipoflavonoids, zinc, manganese, and melatonin are all supplements marketed to improve tinnitus symptoms. However, a cross-sectional study confirmed prior research that did not show any benefit from the use of these supplements.²⁹

Cannabinoids are being studied for their proposed antiepileptic effects. There is a popular misconception of *Cannabis* as a singular chemical when in fact, it is a plant that contains hundreds of chemicals that each act differently on the brain. In a review, Smith and Zheng³⁰ explain that two cannabinoid receptors, CB1 and CB2, are represented, and exert their effects, in different areas of the brain. CB1 receptors block calcium influx in presynaptic terminals, resulting in an inhibitory effect on neurotransmitter release.

CB1 receptors have been found in the dorsal cochlear nuclei, prompting research interest in how cannabinoids affect neurotransmission of unwanted sounds of tinni-

tus. To date, however, there are conflicting data concerning the benefit of cannabinoids and tinnitus. In fact, Smith and Zheng state that some data suggest that cannabinoids might make tinnitus worse.³⁰

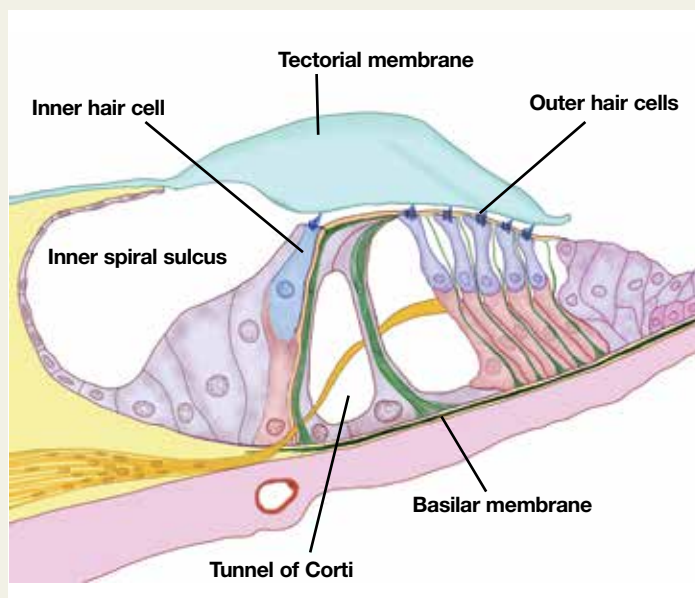
Nonpharmacotherapeutic management

Cognitive behavioral therapy. Conceptualized by Aaron T. Beck in the 1960s, cognitive behavioral therapy (CBT) is the leading recommendation made by the AAO-HNS in its tinnitus treatment guidelines.⁶ Beck's work centered on the idea that behaviors are modifiable thoughts, through analysis of past experiences and assumptions based on those experiences. By understanding the core belief that a patient attaches to a feeling, Beck hypothesized that behaviors or responses to those feelings could be changed; this is accomplished through discussion to dispel unwarranted fears and by teaching coping mechanisms, such as relaxation. The idea behind CBT in the management of tinnitus is clear: The sound cannot be eliminated, but the patient's response to the sound can be modified. Ultimately, through this modified response or habituation, the patient can relax and live with the sound.³¹

transfer; in some cases, however, this does not happen and tinnitus results.¹⁵

Møller describes this change in the behavior of neural activity as *maladaptive plasticity* and states that the learned neural response operates independently from the peripheral auditory input.¹⁶ His research is corroborated by Shore and colleagues, who maintain that “maladaptive neural plasticity appears to underlie these neural changes, as it results in increased spontaneous firing rates and synchrony among neurons in central auditory structures that may generate the phantom percept.”¹²

Today, with state-of-the-art functional MRI (fMRI) and research on the resting-state connectivity approach to fMRI, there is better understanding of the relationship among the amygdala, cortical structures, and the auditory cortex in human subjects. Jastreboff’s neurophysiologic model is supported by the positive results explored in resting-state connectivity with fMRI.¹⁷



Since anxiety, depression, and insomnia are common comorbidities of tinnitus, a psychologic approach remains in the forefront of treatment recommendations. Hoare and colleagues reported that in “a meta-analysis of 10 randomized trials evaluating different forms of CBT (by the therapist and over the Internet), CBT improved tinnitus symptoms compared to non-CBT controls.”⁷

Tinnitus retraining therapy (TRT) is another form of habituation therapy, introduced by Jastreboff in the 1990s. His work furthered the idea that tinnitus could be reframed, as it is in CBT. Simply, he proposed that systems outside the auditory complex—namely the autonomic nervous system and the limbic system—respond to the signal produced by damaged hair cells in the cochlear nuclei. TRT retrains connections to block or ignore these signals.¹³ Unlike CBT, the aim of TRT is to eliminate the *perception* of sound.

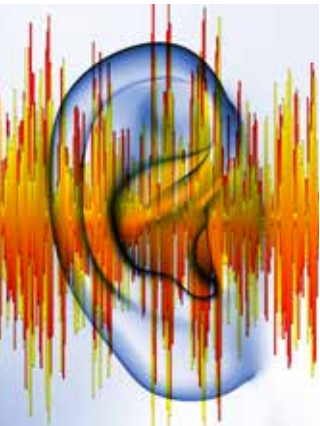
By educating patients about the physiologic mechanisms of tinnitus, TRT reduces patient anxiety related to the sound. The process of habituation follows counseling. To accomplish this, the patient wears a sound generator, similar in appearance to

hearing aids, using broadband noise. The sound does not mask the tinnitus but closes the gap between silence and the perception of tinnitus. The sound generator is worn for six hours daily for approximately 12 months.

Multiple studies have employed Jastreboff’s original technique, including a clinical trial by Bauer and colleagues. The published outcome of this study confirmed that patients experienced a positive and lasting effect with TRT.³² In addition, a small study of TRT conducted by Barozzi and colleagues, using different colors of sound (ie, how the frequency of a given sound corresponds to the light-wave frequency of a particular color), found statistically significant improvement. Allowing patients to pick a sound that they found more pleasant increased the effectiveness of the treatment.³³ (Patients can learn more about TRT by visiting www.tinnitus-pjj.com, hosted by tinnitus researcher Pawel J. Jastreboff.)

Alternative nonmedical therapies have become popular; they include meditation, yoga, physical therapy, mindfulness, and tinnitus-masking treatment with sound.

Results of a study of **yoga** and **meditation** showed that patients felt more relaxed,



Almost one-third of patients complain of debilitating symptoms that can also result in neurocognitive decline—making tinnitus a condition that cannot be ignored.

but that these interventions had no effect on the severity of tinnitus. The principle behind yoga practice, according to K ksoy and colleagues, is that the discipline is thought to affect the limbic system by deactivating the sympathetic response to stimulation from surrounding sounds. In addition, K ksoy states, other researchers have provided evidence that yoga increases circulating levels of antioxidants, which in turn reduce oxidative stress.³⁴

Particularly among members of the millennial generation, **mindfulness** has become a buzzword. The practice refers to a “method for facing, exploring, and alleviating suffering by relating to present experiences.”³⁵ Roland and colleagues conducted a clinical trial of mindfulness practiced by a cohort of patients with bothersome tinnitus; results were based on scores gleaned from standard rating scales (eg, Global Bothersome Scale, Cognitive and Affective Mindfulness Scale-Revised, Cognitive Failures Questionnaire, Tinnitus Handicap Inventory, and Tinnitus Functional Index). Evaluated before and four weeks after cessation of therapy, subjects reported that tinnitus bother was reduced, but none showed statistically significant improvement in depression, anxiety, or cognitive ability.³⁵

Used for more than 40 years, **sound-based therapy** has been discussed in conjunction with TRT.³⁶ It is recognized as an approved but optional treatment by the AAO-HNS. In response to a 2010 study by Hobson that used sound-based therapy alone for tinnitus, Tunkel and colleagues cautioned that the modality showed little benefit. The major downside to acoustic therapy, according to the AAO-HNS clinical guidelines, is cost and patients’ excessive expectation of effectiveness.⁶

According to the AAO-HNS, **repetitive-transcranial magnetic stimulation** is not supported as a valid treatment for tinnitus because it can lead to seizures in patients who are taking medication that lowers the seizure threshold or who have a secondary cause of tinnitus, such as a tumor—therefore creating risk that outweighs any benefit.⁶

CONCLUSION

For a large percentage of the population, chronic subjective tinnitus is a significant variable in the evaluation of quality of life. The condition is not completely understood and often displays features unique to the individual. Much of the initial response to research linking tinnitus with shared pathways typical for chronic pain, anxiety, and depression has resulted in pharmacotherapeutic management that is not always warranted—or successful.

Clinical research into the pathophysiology of tinnitus is providing a better understanding of the neurophysiologic mechanisms that underpin the science of chronic tinnitus. With this information, researchers can one day design medical management that targets specific receptors, resulting in greater management success.

The psychologic impact of tinnitus cannot be underestimated. When almost one-third of patients complain of debilitating symptoms that can also result in neurocognitive decline, tinnitus becomes a condition that cannot be ignored. Guidelines set forth by the AAO-HNS state that CBT and TRT offer some reprieve from symptoms and teach patients habituation without further damage to hearing. The use of broad-based sound generators has been well established as a useful management tool, although it is not curative.

The limitations of some studies that reviewed alternative medicines include small sample size and difficulty comparing research analysis because of disparities in tinnitus rating scales. Also, age bias, comorbid conditions, and study drop-out rates affected overall statistical significance of some studies. Additional, high-quality research is warranted in this area.

Prevention of tinnitus through education on hearing loss and its causes should be regarded as implicit; occupational noise and recreational use of music devices put people at heightened risk for hearing loss and tinnitus. Information and open discussion that include the discovery of tinnitus symptoms during routine physical examination are recommended.

Last, providers who adhere to recognized guidelines will aid patients in coping with the challenges that tinnitus presents. As research continues to unravel the complex interaction between neurons, medical science is hopeful that curative treatments will become available. **CR**

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