Tinnitus and its current treatment—Still an enigma in medicine

Santosh Kumar Swain a,*, Saumyadarshan Nayak b, Jayprakash Russel Ravan c, Mahesh Chandra Sahu d

a Department of Otorhinolaryngology, IMS and SUM Hospital, Siksha "O" Anusandhan University, Kalinganagar, Bhubaneswar, Odisha, India
b Department of Neurology, IMS and SUM Hospital, Siksha "O" Anusandhan University, Kalinganagar, Bhubaneswar, Odisha, India
c Department of Neuropsychiatry, KIIMS, Bhubaneswar, Odisha, India
d Central Research Laboratory, IMS and SUM Hospital, Siksha "O" Anusandhan University, Kalinganagar, Bhubaneswar, Odisha, India

Received 12 August 2015; received in revised form 23 November 2015; accepted 24 November 2015

Introduction

Tinnitus is defined as a perception of sound in proximity to the head with the absence of an external source. The term tinnitus originated from the Latin word 'tinnire', which means 'to ring'. Approximately 15% to 20% of the world’s population suffer from tinnitus and in 25% of the affected population, the condition interferes with daily activity; no effective drug therapy is available for this elusive disease, although much research work into mechanism and possible treatment is underway. As yet, there are no Food and Drug Administration approved drugs available and the quest for a new treatment option for tinnitus focus on important challenges in tinnitus management. A number of options have been used to treat patients with tinnitus, but outcomes have been limited. A new, curative modality will provide a turning point in the management of tinnitus. The purpose of this review article is to discuss the pathophysiology, global burden, current treatment, and prevention of tinnitus, with future prospective studies in new drug therapy for this elusive condition.

Copyright © 2015, Formosan Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
quality of life is severely affected in 1% to 3% of cases. Risk factors include hearing loss, ototoxic medication, head injury, and depression. Tinnitus has traditionally been considered as an otological etiology, but advances in neuroimaging techniques along with development of animal models has increasingly shifted studies toward its neurological correlation.

There are two categories of tinnitus. Subjective tinnitus is the perception of sound in the absence of an acoustic stimulus and is heard only by the sufferer, whereas objective tinnitus is the generation of the sound near the ear that can be heard by the examiner using the stethoscope. Subjective tinnitus is more common and occurs with almost any ear disorder. Objective tinnitus is an uncommon occurrence, usually heard by the examiner, commonly caused by turbulent blood flow or by spontaneous contractions of the muscles in the soft palate or middle ear.

The primary goal of tinnitus treatment is to improve quality of life rather than provide an absolute cure. In patients with tinnitus, quality of life can be improved by treating the comorbidities, such as hearing impairment, depression, insomnia, and anxiety. Currently, the most widely used treatment is counseling, and the best evidence supports the pathophysiology of tinnitus promote the innovative brain-based treatment approach by targeting the neuronal correlates of tinnitus.

Pathophysiology of tinnitus

The pathophysiology of tinnitus is one of the most controversial issue in medical science. Tinnitus is associated with several risk factors, such as prolonged noise exposure (22% of cases), head/neck injury (17% of cases) and infections (10% cases). The newer pathophysiology theory suggests that the central nervous system is the source or generator of tinnitus. Functional magnetic resonance imaging and positron emission tomography scan of the inner ear and brain show a loss of cochlear input by cochlear hair cell damage or a lesion of the auditory nerve to the central auditory system can lead to abnormal neural activity in the auditory cortex area.

It is now known that approximately 24% of tinnitus cases occur due to abnormalities within the inner ear and vestibulocochlear nerve, 35% originate due to abnormalities in the acoustic pathway, and 41% cases have origin with the supratentorial structures. An increase in excitation or a decrease in inhibition may cause an excitatory-inhibitory imbalance, lead to hyperexcitability in these regions, and perception of the tinnitus (Figure 1). Certain neurotransmitters and neuromodulators facilitate the neuronal excitability acting over voltage gated channels, and thus create potential pharmacological targets.

Global burden of tinnitus

In a large epidemiological survey in Norway, 21.3% of men and 16.2% of women reported tinnitus, among whom 4.4% of men and 2.1% women reported high-intensity tinnitus. Epidemiological data show similar results not only seen in other European countries, the United States, and Japan, but also in low-income or middle-income countries such as Africa and Asia. These data show that tinnitus is now a global burden. Increasing age, sensorineural hearing loss, and male sex have been seen as the most relevant risk factors for the origin of tinnitus. Because of the increase in professional and leisure noise with demographic development, the prevalence of tinnitus is expected to increase. In addition, it is a frequent aftereffect of modern warfare.

Treatment of tinnitus

Because of the many etiologies and complex pathophysiology of tinnitus, definitive treatment is yet to be developed. Before treatment can be attempted, proper clinical assessment including a detailed history, measurement of the amount of hearing loss, quantification of tinnitus severity (Figure 2), and identification of etiological factors (Figure 3), associated symptoms, and comorbidities should be performed.

Intravenous lidocaine seems to be effective in some patients with tinnitus; however, the effect is transient and the route of administration not practical in a clinical setting of a chronic condition; therefore, its additional side effects forced its withdrawal from use. Antidepressants are commonly prescribed to treat patients because tinnitus is often associated with depressive disorders. Of all antidepressants, the tricyclic group of drugs is used because of their analgesic effect. This property of tricyclic antidepressant is helpful in view of the proposed etiological similarities between tinnitus and neuropathic pain. Nortriptyline is effective in decreasing the loudness and severity of the tinnitus but is less effective in nondepressed patients. Treatment of tinnitus with benzodiazepines has some benefit. However, due to its adverse effect on regular intake, their routine use cannot be recommended for treatment of tinnitus. Glutamate is an excitatory neurotransmitter in the auditory system. However, various glutamate antagonists such as memantine, flutirpine, and nereimexane have not been beneficial in patients with tinnitus. Investigations into the effectiveness of glutamate antagonists continue. Treatment with intravenous caroverine, an antagonist of non-N-methyl-D-aspartic acid (NMDA) and NMDA receptors, has been studied, with contradictory outcomes.

Sometimes patients with tinnitus have depression or anxiety associated with elevated serum serotonin. Serotonin and γ-aminobutyric acid receptors are present in the auditory system and have been thought to play a role in some cases. Anxiolytic (e.g., diazepam) antidepressants (e.g., amitriptyline), anticonvulsants (e.g., clonazepam), diuretics, and antihistamines (e.g., dexchlorpheniramine maleate) all have shown inconsistent and inconclusive results.

Ginkgo biloba is one of the popular complementary and alternative medicine used by many physicians, but a large trial failed to yield definitive success.

Although betahistine improves cochlear blood flow, there is no evidence suggesting that it is effective in the tinnitus associated with Ménière disease or in other types of tinnitus. Melatonin can help in patients with insomnia associated with tinnitus. It has been suggested that dietary intake of vitamin B, zinc, and magnesium can help.
for tinnitus. There are multiple nonpharmacological treatment options available, such as tinnitus retraining therapy (TRT), masking, amplification, and limiting inducing agents and environmental factors. Masking usually covers or partially covers the tinnitus with an external sound. The sound used for masking is usually less bothersome than the tinnitus. Masking devices are made to generate low-level sounds that decrease the perception of tinnitus. However, in some patients worsening of their tinnitus occurs.

TRT includes counseling and sound generator therapy and is more effective than masking. The concept behind TRT is bypassing or overriding abnormal auditory cortex neural pathways, the pathophysiology postulated to drive tinnitus. The auditory neural pathways play a vital role in tinnitus and also induce habituation to the tinnitus signal. The aim of this therapy is to reach a stage in which patients with tinnitus are unaware of their condition unless they consciously focus on it. Here, the habituation is achieved by directive counseling along with low-level noise generated...
by wearable generators and environmental sounds. Significant improvement has been seen in up to 80% of the cases but no well-controlled studies have been reported. The long-term effect of TRT is not well known, and outcome evaluation can take up to 1 to 2 years.24

Biofeedback or relaxation techniques help patients with tinnitus control certain autonomic functions of the body. The aim of the biofeedback technique is to manage the tinnitus-associated distress by changing the patient’s reaction to it, leading to reductions in tinnitus.27 Cognitive behavioral therapy is usually done by a psychologist. The patient with tinnitus is trained to cope with the condition, and this therapy attempts to change the way the patient thinks about his or her tinnitus. By decreasing the negative thoughts for tinnitus, its annoyance can be minimized. This technique alters the psychological response to tinnitus by identifying and reinforcing coping strategies, and relaxation and distraction techniques. Large studies reported benefit in many patients in reducing tinnitus-related distress, but not much help in decreasing the loudness of the tinnitus.27

Hearing aids are often used by patients with tinnitus and hearing loss to compensate for the absence of auditory input in the impaired frequency range. Amplification of sound with hearing aid is confined to the high-frequency range and will not help in patients with complete absence of inner ear hair cells. In patients with bilateral profound sensorineural hearing loss and tinnitus, a significant suppression of tinnitus has been reported after hearing loss was restored by cochlear implant.28

Surgery has a small but definite role in case of tinnitus treatment. It has a place in regard to pulsatile tinnitus and associated specific clinical conditions such as otosclerosis or Ménière disease. Surgery for neurovascular decompression is beneficial when blood vessels are pressing the auditory nerve. More than 80% of patients with bilateral profound sensorineural hearing loss have tinnitus. A cochlear implant eliminates tinnitus in up to 86% of these patients, although 9% show worse postoperative tinnitus.28

During management of tinnitus, assessment of hypertension, lipid profiles, thyroid function tests, allergies, and factors aggravating tinnitus such as stress, caffeine, aspirin, and nicotine intake.29 If any of these levels or conditions is abnormal, they should be treated before the tinnitus. Embolization or ligation should be used to treat a vascular anomaly such as arteriovenous malformation. The use of hearing aids and cochlear implants to treat sensorineural hearing loss with cessation of offending medications is also an important aspect of tinnitus treatment.

Acupuncture, herbal remedies such as Ginkgo biloba, ear candling, low-power lasers, and electromagnetic stimulation all have been used to treat tinnitus but with little evidence of benefit.30 Tinnitus of "low buzz" type often

---

**Figure 3** Identification of etiological factors from clinical presentations with its treatment options.
associated with temporomandibular joint dysfunction (TMD) can affect the Eustachian tube and tympanic structures. Laser acupuncture is an innovative treatment option for TMD because it is noninvasive, results in partial or total relief of pain, and has no complications.

Subjective tinnitus due to stapedius myoclonus syndrome is rare and severely affects daily activities such as eating, talking, and walking. It may be treated with noise masking, anticonvulsant agents, or myotonytomy but has very good result with the addition of botulinum toxin A.

Drugs in the pipeline for patients with tinnitus

Neurokinin receptors are present in the inner ear, which has a potential therapeutic target for treating tinnitus. Vestipitant is an antagonist of the neurokinin-1 receptor, which usually binds substance P. Vestipitant and the combination of paroxetine and vestipitant are currently under clinical trials for treating patients with tinnitus.

A nonsterile patch (LidoPAIN TV, EpiCept) has been developed for delivery of lidocaine applied over preauricular skin. Its clinical efficacy is also under clinical trial. Neramexane is a noncompetitive, voltage dependent nonselective NMDA antagonist that blocks the nicotinic cholinergic receptors present on the hair cells of the inner ear. This drug is also in clinical trials for determining its efficacy, tolerability, and safety.

Prevention

Significant loud noise, ototoxic drugs, and cytotoxic drugs are risk factors for the development of tinnitus. These risk factors cause damage to the cochlear hair cells by apoptosis rather than necrosis. Currently, research is focused on identifying agents that block the apoptosis. The use of antioxidants is now an area of interest, with D-methionine or a combination of betacarotene, vitamin C, and vitamin E showing initial promise. Cochlear insult can be repaired or a combination of betacarotene, vitamin C, and vitamin E identifying agents that block the apoptosis. The use of stem cell therapy and gene therapy. Smoking, excessive alcohol or caffeine intake, or central nervous system. Drugs such as aspirin should be stopped or the alternative drug may be started after proper counseling the patient.

Conclusion

The successful treatment of tinnitus depends on a team comprising an otolaryngologist, audiologist, neurologist, psychologist, and sleep or pain specialists. Even with progress in the understanding of the pathophysiology of tinnitus, treatment modalities still focus on minimizing the awareness of tinnitus and its effect on quality of life rather than a definitive cure. Although we are far away from an exact understanding of the pathophysiology of tinnitus, the treatment options are much more encouraging than a decade ago. Due to medical advancement with molecular, biochemical, and imaging techniques, important insights into the underlying etiology of tinnitus have occurred. Currently, patients show improvement with counseling, cognitive behavioral therapy, and additional use of different sound therapy; however, many prefer drug therapy that would lead to complete suppression of tinnitus. Looking towards the future treatment of tinnitus, the development of new molecular treatment for complete cure of tinnitus will be an important goal.

Acknowledgments

The authors are grateful to Dr. R.N. Padhy, HOD, Central Research Laboratory and Dr. D.K. Roy, Medical Director, IMS and SUM Hospital, SOA University, Bhubaneswar, Odisha, India for their guidance in research activities and encouragement.

References


