Journal of the Formosan Medical Association (2016) 115, 139–144

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

REVIEW ARTICLE

Tinnitus and its current treatment—Still an enigma in medicine

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

KEYWORDS
pathophysiology;
tinnitus;
tinnitus retraining therapy;
treatment

Tinnitus is a phantom auditory perception that occurs in humans. Tinnitus, which is a distressing problem affecting many people around the world, is commonly referred to as ringing in the ears. 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.

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'.[1] 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;

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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http://dx.doi.org/10.1016/j.jfma.2015.11.011

quality of life is severely affected in 1% to 3% of cases.[2] 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 sufferers, whereas objective tinnitus is the generation of the sound near the ear that can be heard by the examiner using the stethoscope.[3] 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 is seen with cognitive behavioral therapy. New insights into 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).[4] The newer pathophysiology theory suggests that the central nervous system is the source or generator of tinnitus.[5] 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.[6]

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 within the supratentorial structures.[7] 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.[8]

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.[9] 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.[10] 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.[11] Because of the increase in professional and leisure noise with demographic development, the prevalence of tinnitus is expected to increase.[12] In addition, it is a frequent aftereffect of modern warfare.[13]

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.[14] 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.[15] This property of tricyclic antidepressant is helpful in view of the proposed etiological similarities between tinnitus and neuropathic pain.[16] Nortriptyline is effective in decreasing the loudness and severity of the tinnitus but is less effective in nondepressed patients.[17] 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.[18] Glutamate is an excitatory neurotransmitter in the auditory system. However, various glutamate antagonists such as memantine, flutirpine, and neremexane have not been beneficial in patients with tinnitus.[19] 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.[20] 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.[2] Ginkgo biloba is one of the popular complementary and alternative medicine used by many physicians, but a large trial failed to yield definitive success.[21]

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.[22] Melatonin can help in patients with insomnia associated with tinnitus.[23] It has been suggested that dietary intake of vitamin B, zinc, and magnesium can helpful