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Tinnitus, an updated review.

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Abstract:

Tinnitus is defined as the perception of sound in the absence of an external source. This symptom can be classified as subjective (experienced only by the patient) or objective (experienced by the patient and perceived by the physician). Severe tinnitus is one of the main causes of disability and affects approximately 10% of the population at some time in their life.

This symptom is mostly caused by cochlear damage or as a result of damage in the auditory pathway. It is present as a symptom in multiple diseases in otolaryngology, so the diagnosis and treatment methods are specific to each etiology.

It is necessary to perform an adequate clinical history, an otolaryngologic examination, exploration of the temporomandibular joint, tonal audiometry, high-frequency audiometry, pitch masking, loudness masking and minimum masking level to assess tinnitus and to determine its etiology.

There is no single treatment that encompasses all forms of tinnitus. The clinical practice seeks to diagnose the subtype to carry out the specific treatment. Current treatments include sound therapy, psychotherapy, pharmacological, physical and surgical therapies.

We reviewed the most recent studies on epidemiology, clinical manifestations, diagnosis and treatment to provide an update on Tinnitus that can help provide an overview for clinical practice and future research.

Keywords: tinnitus, hearing loss, audiometry, cognitive behavioral therapy.

Highlights:

- Tinnitus is the perception of sound in the absence of an external source and can be classified as subjective and subjective.
- Tinnitus is the third most disabling symptom an individual can suffer from
- It has an origin which can be peripheral or central and a perception site.
- The Dorsal Cochlear Nucleus hypothesis is the most accepted for explaining tinnitus.
- Different tests can be performed to address the etiology of the tinnitus.
- A wide variety of treatments have been studied with variable results.

Abbreviation

Dorsal Cochlear Nucleus (DCN), Tinnitus Retraining Therapy (TRT), Behavioral Cognitive Therapy (BCT), N-methyl-D-aspartate (NMDA), Transcranial direct current stimulation (TDCS), Transcranial magnetic stimulation (TMS), Repetitive transcranial magnetic stimulation (rTMS), Deep Brain Stimulation (DBS), Vagus nerve stimulation (VNS)

1 Introduction

Tinnitus is defined as the perception of sound in the absence of an external source, it is a symptom of multiple diseases, and the diagnostic methods and treatment methods are specific to each of them(1).

It was believed to be a purely cochlear disorder and is now recognized as a disorder of the auditory pathway or different areas of the auditory cortex(2). Due to the negative impact on quality of life, it is a common main complaint among general practitioners, neurologists, and otolaryngologists. Tinnitus remains a problem whose etiology is not fully elucidated or its treatment 100% defined.

2 Literature Review

A recent systematic review reports a prevalence of 5.1-42.7%. Surveys report that 10% of the evaluated adults suffer from chronic tinnitus and 5% mention that it negatively impacts on quality of life. On the other hand, 50-90% of adults report the perception of sound in absolute silence. About 75% have experienced sudden unilateral deafness accompanied by tinnitus, lasting less than a minute. The same population reports having presented tinnitus after exposure to loud sounds by 50%(3). The most influential factor in its appearance is the degree of sensorineural hearing loss(4). The risk of developing and the prevalence of tinnitus increases with age. An increase related to noise exposure is expected in the future(5). A systematic review suggests pediatric prevalence, although more difficult to assess, ranges between 3.2-17.1%(6). Another study estimates tinnitus to be present in 25% of children with hearing loss(7).

Otological diseases are accompanied by tinnitus in 85%. The location of tinnitus is variable, more than 50% of patients refer it in both ears, about 35% suffer from it in only one and 15% place it on the head(7).

The majority of patients tend to adapt to their tinnitus, but those who suffer from severe tinnitus usually present frustration, anxiety, depression, cognitive problems, insomnia and stress, severely impacting their quality of life(8). In the United States, it is estimated that tinnitus affects about 40 million people, and a quarter suffers from severe tinnitus. According to the American Tinnitus Association, severe tinnitus represents the third most disabling symptom that an individual can suffer after severe pain and balance disorders (8). With a prevalence of bothersome tinnitus 3.0-30.9%(3). Reported risk factors for tinnitus include: female gender, hearing loss, noise exposure and stress(9).

a) Subjective (95%): Experienced only by the patient in the absence of any external stimulation.

b) Objective (5%): Experienced by the patient and perceived by the examiner. This type has an underlying cause outside the ear, such as vascular flow phenomena (given by arteriosclerosis, arteriovenous shunt, abnormal arterial loop in the internal auditory canal, arterial hypertension) or due to the existence of mechanical compressive elements (tumors, specific conditions of cervical vertebrae or temporomandibular joint)(10).

c) Primary tinnitus: describes idiopathic tinnitus that may or may not be associated with SNHL(11).

d) Secondary tinnitus: tinnitus associated with a specific cause different than SNHL. Its a symptom of various auditory diseases, from external auditory canal pathology, middle ear diseases or cochlear abnormalities(11).

e) Acute: duration of less than 6 months(11).

f) Chronic: duration of more than 6 months(11).

Multiple pathologies are accompanied or could cause tinnitus, such as sudden deafness, acoustic trauma, sensorineural hearing loss, infections of the inner ear, otosclerosis, head trauma, neuroma and tumor in the pontocerebellar angle, Meniere's disease, medications and ototoxic drugs (aspirin, diuretics, aminoglycosides, quinine), antineoplastic drugs, excessive alcohol consumption and stimulants, high blood pressure, severe anemia, kidney failure and psychiatric disorders. Many involve an alteration of the peripheral auditory pathway and others are not related to the ear, but its association with tinnitus due to its connections with the auditory system within the central nervous system(3)(10).

According to several studies, tinnitus to be perceived requires the coexistence of at least two functional elements: An origin, which can be peripheral or central; and a central perception site, which allows cortical integration and conscious perception of tinnitus(10).

Tinnitus can arise from damage at any level of the auditory pathway, but most cases are caused by cochlear damage(5). Findings in experimental animals and clinical observations led to the Dorsal Cochlear Nucleus (DCN) hypothesis as the most convincing model to explain the main characteristics of common tinnitus syndromes. The DCN hypothesis proposes that increased activity of the main output cell of the DCN can cause tinnitus when the threshold is exceeded due to changes in the auditory inputs to the DCN, somatosensory inputs to the DCN, or both(3).

The mechanisms of integration of the auditory-somatosensory information in the DCN may also be relevant for the generation of tinnitus. Dorsal root entrances and trigeminal ganglia that carry somatosensory information end in the cochlear nuclei, and somatosensory stimulation results in immediate and long-term facilitation or suppression of responses to sound in the cochlear nucleus(12). It has also been described that the integration of auditory-somatosensory information, which leads to the modulation of neuronal activity in the central auditory pathways, takes place in the primary auditory cortex(12). This finding may explain the appearance of tinnitus after cervical trauma (13) or with temporomandibular joint disorders(14).

After cochlear damage (for example, due to noise trauma), the loss of internal hair cells that generally transduce a certain frequency of sound in the cochlea leads to peripheral damping. Animal studies have shown that if the loss of hair cells extends over a wide frequency range, it is followed by a tonotopic rearrangement of the primary auditory cortex, where the normally ordered representation of spectral frequencies is altered accordingly(15).

Noise trauma studies in animals show that sensitivity to high frequencies is lost. The cortical neurons that generally selectively respond to frequencies in the range of hearing loss, no longer respond to their designated frequency. Instead, the cortical neuron changes their tuning to respond to frequencies at the edge of the lesion; thus frequencies slightly lower than the lowest of the lost frequencies(16). Tinnitus can develop with little or no hearing loss (approximately 25% of people with tinnitus have a normal audiogram).

In order of giving the best approach the "Tinnitus Research Initiative" meeting reached a consensus in 2006 for the assessment of the patient with tinnitus and the measurement of the results for its correct identification and application of specific treatments.

The objectives of this study were to analyze recent national and international scientific publications on the knowledge of the most basic aspects of tinnitus such as its etiology, epidemiology, diagnosis and treatment searching for the best approach offer.

The articles included were based in the authors criteria after reading the abstract of each article in order to make a complete and current narrative review that compared the evolution of knowledge regarding this condition.

The main goal was to summarize the most recent papers and we only extended our references further back in time in a few cases where we considered the mention of that research was needed.

4 Discussion

For the writing of this review the articles used were searched in the databases of Pubmed and Google Scholar using the following keywords: Tinnitus/ treatment/ epidemiology/ therapy/ hearing loss from 2010 up to 2019, and referenced articles in those selected.

Initially, 448 articles were identified, 102 articles were found in the SciELO database, 346 in the PubMed database; of which we selected 130.

Those within a range of 10 years prior to the present, in English or Spanish, with no similar titles or results, were included for our review's writing having a total of 56.

Our selected literature agree that the evaluation of tinnitus must include the elements of any medical evaluation, association with new medications, psychological stressors, auditory, vestibular or neurologic complaints. Neck discomfort and stress, jaw pain as well as bruxism should be evaluated. The most important features of tinnitus are quality (pulsatile or a clicking component), its location (unilateral or bilateral), its variability (intermittent or constant), its pitch (low or high pitch) and if tinnitus is diminished to alter the characteristics. If the unilateral click is present, the possibility of compression of the auditory nerve should be considered. In the same way, if the tinnitus has a pulsatile character that is in sync with the heart rhythm; if it is bilateral and not always pulsatile, a myofascial etiology is very likely; if it is unilateral and intermittent, in addition to myofascial, vascular compression of the auditory nerve should also be considered(3).

In addition to the neuro-otological examination, the examination of the patient with tinnitus should include inspection of the teeth, listening around the ear for sounds similar to the tinnitus or palpitations of the patients(17).

The US Clinical Practice Guidelines recommend that clinicians may obtain an initial comprehensive audiologic examination in patients who present with tinnitus(18).

Within the applied tests the conventional audiogram or pure tone audiometry must be included, which evaluates frequencies from 250 to 8000 Hz. Values of 20 dB or lower in the tested frequencies are considered normal. Speech audiometry determines the lowest intensity level at which speech is repeated 50% of the time and the percentage of words that are repeated correctly when presented at a suprathreshold level, and its important in the evaluation of the patient(19,20). To evaluate frequencies above 8,000 Hz, high-frequency audiometry or extended audiometry is used (21). High-frequency audiometry was first described in 1960(22) and its usefulness has been demonstrated for the evaluation of ototoxicity in treatment with chemotherapeutics such as cisplatin(23) and as a hearing loss screening due to continuous noise exposure (22)(24). Due to the association between tinnitus and hearing loss, audiometry is also useful for evaluation. Sometimes pure tone audiometry shows no alteration and extended audiometry shows additional useful information that is not found in conventional audiometry (25). Pitch masking, loudness masking and minimum masking level provide the quantitative information about the characteristics of the tinnitus. The results of this tests determine if the tinnitus will be successfully masked by an external sound or noise(19).

The impedance measurement is useful in cases where middle ear pathology is suspected, and otoscopy is doubtful. As well as see fluctuations in pressure produced by muscle contractions or vascular pulsations. Auditory evoked brainstem potentials allow to rule out the presence of retrocochlear disease or high central, although the definitive diagnosis will be defined by an imaging test. Between 1 and 9% of tinnitus is caused by spontaneous acoustic otoemissions. This association is relevant because spontaneous acoustic otoemissions can be suppressed with acetylsalicylic acid(2)(26).

The US Clinical Practice Guidelines state that "clinicians should not obtain imaging studies of the head and neck in patients with tinnitus, specifically to evaluate the tinnitus, unless they have 1 or more of the following: tinnitus that localizes to 1 ear, pulsatile tinnitus, focal neurological abnormalities, or asymmetric hearing loss"(18). The Eco-Doppler will be used to assess the condition of the vasculature probably involved and will help rule out possible stenosis. A computed tomography might reveal bone abnormalities (Paget's disease, tympanic glomus, otosclerosis) and their extent. A magnetic resonance imaging is the imaging test of choice for the assessment of tumor and demyelinating pathology at the level of the central nervous system(10).

Additional questionnaires assess the severity of tinnitus and its impact on life quality. The most recognized disability questionnaires are: Tinnitus Handicap Inventory(27) and the McCombe Severity Graduation Guide (2001), which classifies results in very mild, mild, moderate, severe and catastrophic(28).

There is no single treatment that covers all forms of tinnitus, clinical research attempts to diagnose the subtype to carry out the specific treatment. Different treatments have been proposed, ranging from not invasive to surgical and invasive alternatives. The US clinical guidelines recommend Cognitive Behavioral Therapy (CBT) for persistent, bothersome tinnitus and sound therapy as a treatment option. They state also clinicians should not recommend pharmacological treatment such as antidepressants, anticonvulsants, anxiolytics, or intratympanic medications to every patient for a primary indication of treating persistent, bothersome tinnitus. Finally US Guidelines state that clinicians should not recommend Transcranial magnetic stimulation for the treatment of patients with persistent, bothersome tinnitus(18).

The treatment options are listed and defined in table 1.

Field	Therapy	Research	Author
Sound Therapy	Tinnitus retraining therapy (TRT) Sound Masking	Used to modify the patient's perception and reaction to tinnitus by external noise.	Jastreboff, 2015 (29)
Psychological therapy	Behavioral Cognitive Therapy (BCT)	Helps patients to build positive and realistic thoughts that allow them to cope with their condition focusing on the reduction of distress and disability induced by tinnitus (30).	McKenna, 2017 (30)
Pharmacological Therapy	Anesthetics.	Lidocaine is the only drug capable of suppressing tinnitus. Administered intravenously, its effectiveness varies between 50 to 75% and its improvement rate of 85%. Although is not an option for long term treatment due to its short term effects and potentially life-threatening arrhythmogenic side effects (31,32).	Langguth, 2009(31) Otsuka, 2003(32)
	N-methyl-D-aspartate glutaminergic receptor antagonists.	Decrease the action of glutamate, the main excitatory amino acid of the central nervous system. Glutamate is involved together with its N-methyl-D-aspartate (NMDA) receptors in the rapid synaptic transmission in phenomena of neuronal plasticity, memory and in situations of acute and chronic pain, generating and maintaining states of hypersensitivity or hyperalgesia (33).	Espinosa-Sánchez, 2014 (33)
	Anticonvulsants.	Carbamazepine blocks the Na+ channels and inhibits high-frequency neuronal discharges. At a dose of 50-400 mg/day, it is particularly useful in tinnitus modulated by vascular and nervous compression (for example, anteroinferior cerebellar artery loop in the internal auditory canal) called "typewriter"(34). Carbamazepine and oxcarbazepine are not more effective than placebo in decreasing tinnitus severity (35).	Levine, 2006 (34) Gerami, 2012 (35)
	Antidepressants	Amitriptyline is effective in patients with tinnitus and depression. Nortriptyline in patients with severe and chronic tinnitus, in doses of 20-40mg / day, decreases its intensity. Sertraline significantly decreases the intensity of tinnitus. Cyclobenzaprine is an analog of amitriptyline. It is also a muscle relaxant and particularly useful in myomodulated tinnitus (36,37,38). Different studies suggest patients benefit from antidepressants, this may not be a direct effect on tinnitus, but rather in the depression and anxiety present in patients with tinnitus (31).	Lockwood, 2002 (36) Levine, 2006(37) Robinson, 2007(38) Langguth, 2009(31)
	Benzodiazepines	Clonazepam is effective in rhythmic tinnitus such as myoclonus of the palate and middle ear. Medical records of patients taking clonazepam 0.5-1mg per day for vestibular or cochleovestibular disorders revealed improvement in tinnitus in 32% (39).	Jufas, 2015(39)
	Corticosteroids	Corticosteroids have been used in the treatment of sudden sensorineural hearing loss and in the autoimmune disease of the inner ear. Its intratympanic administration is most commonly used. Its use in tinnitus is still controversial (31).	Langguth, 2009(31)
	Other drugs	Nimodipine dilates cerebral blood vessels, improves blood flow, decreases tinnitus although the quality of evidence is low. Dopamine antagonists (calming effect), H1 antihistamines (subcortical sedative effect), vasodilators and calcium antagonists are among the most prescribed drugs (10). Melatonin has been the subject of multiple studies whose results suggest that its administration may help those patients who have insomnia associated with tinnitus (40). A randomized double-blind study on ondansetron seems to decrease the intensity of the tinnitus and improve hearing (41).	Curet, 2016(10) Rosenberg, 1998(40) Taslimi, 2013 (41)
Physical therapies.	Hyperbaric oxygen therapy	A recent systematic review showed no statistically significant difference in patients with acute and chronic tinnitus treated with hyperbaric oxygenation versus the control group(42). Another study showed ear barotrauma was the most common otological complication in this therapy (95.2 %) and to a lesser extent presented tinnitus (1.8%) (43).	Bennett, 2012(42) Yamamoto, 2016(43)
	Transcranial direct current stimulation (TDCS)	This procedure seeks to increase or reduce neuronal activity by attaching one end of electrodes to the scalp and another end to the current source. Studies suggest 39.5% of all the patients responded to active TDCS, with a reduction of 13.5% of the tinnitus intensity (44). Wang et al. showed in a meta-analysis no benefit in the loudness of tinnitus after TDCS (45). Yuan et al. concluded in their meta-analysis that TDCS has promising treatment outcomes, but so far there is not a standard protocol for tinnitus treatment (46).	Folmer, 2014(44) Wang, 2018(45) Yuan, 2018(46)

	Repetitive Transcranial magnetic stimulation (rTMS)	In a meta-analysis by Soleimani et al, report a moderate efficacy of low-frequency rTMS as a treatment of chronic tinnitus, but stated that their conclusions were based on a small number of trials, and more should be made(47). rTMS over the temporal or temporoparietal cortex have been investigated(48). Kreuzer et al. showed rTMS use in chronic tinnitus, reporting 50% of the patients with immediate effect, although the effects in the tinnitus questionnaire were not statistically significant(49).	Soleimani, 2016(47) Zhang, 2015(48) Kreuzer,2017(49)
	Deep Brain Stimulation (DBS)	Is an invasive method in which long electrodes are implanted in the brain to deliver electrical impulses to a specific region. A stimulator unit is implanted in the skin and an external device is used to control the stimulator, delivering electrical current through the wires to the electrodes(44). Animal models have shown that this procedure can modulate tinnitus and show a possible application for this entity(50).	Folmer, 2014(44) Ahsan, 2018(50)
	Brain Surface Implants	Electrodes near the surface of the brain can be used to affect specific neural regions. Some studies have shown mixed results. It is important to consider the risks and benefits of this procedure (44).	Folmer, 2014(44)
	Vagus nerve stimulation (VNS)	Is a surgical implant procedure for the treatment of epilepsy and depression, it triggers the release of neuromodulators that enhance plastic changes in the cerebral cortex. Studies involving VNS paired with tones show this therapy could be useful, although larger studies are needed (51,52).	De Ridder, 2015(51) Ylikoski, 2017(52)
Surgical Approaches	Cochlear implantation	Is a common treatment for sensorineural hearing loss, and is often reported as an additional benefit of subjective tinnitus (53). Birger Mo et al. (54) in 2002 published in a wide series of 83 patients with cochlear implants and tinnitus, which is reduced in 54% of patients, and in the control group of 60 patients using hearing aids decreased in 41%. Ramos et al. (55) consider that the reduction of tinnitus after cochlear implantation may be due to several mechanisms, such as habituation, acoustic masking, direct stimulation of the cochlear nerve and reorganization of cortical areas. Although more studies are needed, the cochlear implant seems to be an effective method for the treatment of disabling tinnitus in patients with severe unilateral severe-profound hearing loss.	Ramakers, 2015(53) Birger, 2002(54) Ramos, 2012(55)
Treatment response evaluation	Functional Tinnitus Index (TFI)	Henry et al. (11) in 2014 developed and validated a self-report questionnaire, the TFI. Highly sensitive to the effects of the treatments used according to their responsiveness, addressing the main positive and negative characteristics of the impact of tinnitus. The TFI has eight subscales that address tinnitus intrusion, the patient's sense of control, cognitive interference, sleep disorder, hearing problems, relaxation problems, quality of life and emotional distress. They also include general guidelines to help facilitate the interpretation of TFI scores.	Henry, 2015(11)all of the TRC objectives were met, with the final 25-item Tinnitus Functional Index (TFI

Table 1: Literature review of treatment in tinnitus.

As far as prevention respects it is necessary to reduce exposure to ototoxic treatments and significant noise, as risk factors for the development of tinnitus are recognized. These factors are known to cause the death of the hair cells of the cochlea by apoptosis, rather than by necrosis(56).

5 Conclusion

Tinnitus is one of the most disabling symptoms in otolaryngology and is present in the majority of otological diseases. Around 10% of the population lives with tinnitus or has suffered from it.

As of now, the most accepted hypothesis of its pathophysiology is the DCN hypothesis. It states that increased activity of the main output cell of the DCN can cause tinnitus when a threshold is exceeded due to changes in the auditory inputs to the DCN, somatosensory inputs to the DCN or a combination of both. Further research is needed to find the exact pathophysiology of this entity.

It is necessary to make a complete evaluation of the patient including clinical history and otolaryngologic exploration and perform audiometric tests because it could be associated with underlying hearing loss.

Because their etiology is multiple and there is no single treatment and it is generally holistic. It is necessary to carry out more studies about tinnitus and thus be able to determine as to what is the most effective form of treatment, although the treatment should be individualized for each patient.

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