



Current treatments for tinnitus

Tratamientos actuales para el tinnitus

Tratamentos atuais para tinnitus

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ABSTRACT

Objective: Explore tinnitus treatment approaches. **Bibliographic review:** Tinnitus is the perception of sound without an external source, impacting public health and correlating with depression. Medications (e.g., tricyclic antidepressants, benzodiazepines, anticonvulsants, melatonin) show some effectiveness in reducing tinnitus severity, but their efficacy is uncertain. Non-pharmacological therapies like cognitive-behavioral therapy (CBT) and tinnitus retraining therapy (TRT) hold promise in managing symptoms. CBT targets cognitive and behavioral aspects, while TRT combines sound therapy and counseling for habituation. Cochlear implant and stapes surgeries also improve tinnitus perception. Neuromodulation techniques (e.g., transcranial magnetic stimulation, transcranial direct current stimulation) are being explored, but research is needed for efficacy confirmation. **Final considerations:** Effective treatment options are crucial for tinnitus patients' quality of life. Pharmacological approaches (e.g., antidepressants, benzodiazepines, anticonvulsants) offer potential, although efficacy is uncertain. Non-pharmacological treatments like CBT, TRT, cochlear implantation, stapes surgery, and transcranial magnetic stimulation show promise in reducing tinnitus severity and improving well-being.

Keywords: Tinnitus, Antidepressive agents, Benzodiazepines, Cognitive behavioral therapy.

RESUMEN

Objetivo: Explorar enfoques de tratamiento para el tinnitus. **Revisión bibliográfica:** El tinnitus es la percepción de sonidos sin una fuente externa, afectando la salud pública y correlacionando con la depresión. Los medicamentos (por ejemplo, antidepresivos tricíclicos, benzodiazepinas, anticonvulsivos, melatonina) muestran cierta eficacia en la reducción de la gravedad del tinnitus, pero su eficacia es incierta. Terapias no farmacológicas como la terapia cognitivo-conductual (TCC) y la terapia de reentrenamiento del tinnitus (TRT) ofrecen promesas en el manejo de los síntomas. La TCC se enfoca en los aspectos cognitivos y conductuales,

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mientras que la TRT combina terapia de sonido y asesoramiento para la habituación. La cirugía de implante coclear y la cirugía del estribo también mejoran la percepción del tinnitus. Técnicas de neuromodulación (por ejemplo, estimulación magnética transcraneal, estimulación transcraneal de corriente directa) están siendo exploradas. **Consideraciones finales:** Opciones de tratamiento efectivas son cruciales para la calidad de vida de los pacientes con tinnitus. Enfoques farmacológicos (por ejemplo, antidepresivos, benzodiazepinas, anticonvulsivos) son opciones viables. Tratamientos no farmacológicos como la TCC, TRT, implantación coclear, cirugía del estribo y estimulación magnética transcraneal muestran promesas en la reducción de la gravedad del tinnitus y mejora del bienestar.

Palabras clave: Tinnitus, Agentes antidepresivos, Benzodiazepinas, Terapia cognitivo-conductual.

RESUMO

Objetivo: Explorar abordagens de tratamento para zumbido. **Revisão bibliográfica:** O zumbido no ouvido é a percepção de som sem uma fonte externa, impactando a saúde pública e correlacionando-se com a depressão. Medicamentos (por exemplo, antidepressivos tricíclicos, benzodiazepínicos, anticonvulsivantes, melatonina) mostram alguma eficácia na redução da gravidade do zumbido, mas sua eficácia é incerta. Terapias não farmacológicas, como a terapia cognitivo-comportamental (TCC) e a terapia de reabilitação do zumbido (TRZ), mostram promessa no manejo dos sintomas. A TCC aborda aspectos cognitivos e comportamentais, enquanto a TRZ combina terapia sonora e aconselhamento para habituação. Implantes cocleares e cirurgias de estapes também melhoram a percepção do zumbido. Técnicas de neuromodulação (por exemplo, estimulação magnética transcraniana, estimulação transcraniana por corrente contínua) estão sendo exploradas, mas pesquisas são necessárias para confirmar sua eficácia. **Considerações finais:** Opções de tratamento eficazes são cruciais para a qualidade de vida dos pacientes com zumbido no ouvido. Abordagens farmacológicas (por exemplo, antidepressivos, benzodiazepínicos, anticonvulsivantes) oferecem potencial, embora sua eficácia seja incerta. Tratamentos não farmacológicos, como TCC, TRZ, implante coclear, cirurgia de estapes e estimulação magnética transcraniana, mostram promessa na redução da gravidade do zumbido e na melhoria do bem-estar.

Palavras-chave: Tinnitus, Agentes antidepresivos, Benzodiazepinas, Terapia cognitivo-conductual.

INTRODUCTION

Tinnitus is a condition characterized by the perception of sound (*i.e.* ringing) in the absence of an external source. It is considered an important public health challenge that affects approximately twenty-eight million Brazilians and fifty million Americans (LIMA DO, et al., 2020;). The prevalence is higher among older adults, non-hispanic whites, former smokers, exposure to loud noise, adults with hypertension, hearing impairment, and anxiety disorder, and can vary among different studies. (EGGERMONT JJ and ROBERTS LE, 2012; SHARGORODSKY J, et al., 2010; MCCORMACK A, et al., 2016; BHATT JM, et al., 2016).

Notably, tinnitus was more prevalent in men (10.5%) compared to women (8.8%). Moreover, individuals who consistently encountered loud noises at their workplaces or during recreational activities were more likely to report higher rates of tinnitus. Merely 49.4% of those affected by tinnitus had sought consultation with a physician regarding their condition, with medications being the most commonly recommended treatment option (45.4%). Conversely, interventions such as hearing aids, wearable and nonwearable masking devices, and cognitive behavioral therapy were discussed less frequently (BHATT JM, et al., 2016).

It is a common clinical entity that is frequently associated with co-existing hearing loss. It severely affects the quality of life of individuals, and its prevalence seems to increase with age. Hearing evaluation with pure tone audiometry and measurement of quality of life are important assessments when dealing with tinnitus patients (SWAIN SK, 2021). Even though the pathophysiology of tinnitus still remain unclear, it is speculated that the interaction of different parts of the central nervous system, limbic system and cochleae produce an

abnormal neuronal activity perceived by the patient as a ringing sound (TZOUNOPOLOUS T and HENTON A, 2021). Research has demonstrated a notable correlation between tinnitus and depression, as it may have considerable impacts on a patient's personal life, emotional well-being, and social functioning. Both conditions present similar levels of prevalence, and many studies have observed an additive effect of both on the quality of life in those suffering from tinnitus (HUSAIN FT, 2020). Other manifestations include difficulties with auditory attention ability, headache and sleeplessness. A variety of personality disorders, (e.g. hysteria, hypochondriasis) social withdrawal and emotional isolation may also be observed (SWAIN SK, 2021; LIMA DO, et al., 2020).

It is a widespread public health concern that affects millions of individuals. It has a significant impact on a patient's emotional, social, and personal well-being, causing depression, difficulty with auditory attention, headache, and sleeplessness. Therefore, identifying effective treatment options for tinnitus is crucial in improving patients quality of life. It is important to address the diverse manifestations and related conditions of tinnitus to develop targeted and personalized treatment plans. By doing so, individuals suffering from tinnitus can receive the care they need to manage and improve their symptoms. This narrative review aims to critically examine the most recent evidence available in the literature related to both pharmacological and non-pharmacological treatment approaches.

BIBLIOGRAPHIC REVIEW

Pharmacological Treatments for Tinnitus

Observations have shown that 80% of patients with severe tinnitus exhibit depression, indicating a possible correlation. Tricyclic antidepressants (TCAs) such as nortriptyline and amitriptyline reduce depression, tinnitus disability scores, and tinnitus loudness in patients with serious tinnitus and depression. TCAs and selective serotonin reuptake inhibitors (SSRIs) have been effective for tinnitus with depression, anxiety, or insomnia. TCAs and heterocyclic antidepressants (e.g. trazodone) caused important side effects, and trazodone demonstrated no effectiveness. Although literature reviews suggest antidepressants may benefit tinnitus patients, the efficacy of these agents remains uncertain (KIM SH, et al., 2021).

A Network Meta-Analysis of 36 randomized controlled trials (RCT's) by Chen JJ, et al. (2021) compared the efficacy of brain-acting agents (e.g. amitriptyline, acamprosate, gabapentin and memantine), anti-inflammation/antioxidant agents (intra-tympanic dexamethasone injection plus oral melatonin, N-acetylcysteine, oral magnesium), pentoxifylline, baclofen, thyroxine and other agents. Among the treatments examined, oral amitriptyline displayed the highest improvement in tinnitus severity and the fourth highest response rate. The paper has limitations such as low-quality included studies with high risk of bias, small sample sizes impacting statistical power, varying treatment durations and follow-up periods, high heterogeneity among studies, and a lack of consideration for potential side effects of the investigated treatments.

Benzodiazepines (BDZs) and other anxiolytic agents are commonly prescribed for tinnitus. BDZs, which enhance GABA activity by binding to GABA receptors, inhibit the spread of tinnitus to auditory centers, alleviating anxiety, depression, and promoting sleep. However, long-term use of BDZs may lead to dependence, sedation, ataxia, and depression, and the risk of misuse and central nervous side-effects limits their use. Compared to placebo, treatment with 30 mg/day of oxazepam improved tinnitus in 52% of patients, while 0.5 mg of clonazepam thrice a day significantly improved tinnitus in 69% of patients. BDZs with longer half-lives, such as diazepam and oxazepam, have no therapeutic effect on tinnitus, while clonazepam improves tinnitus loudness, duration, annoyance, and Tinnitus Handicap Inventory (THI) score. Therefore, BDZs, especially those with shorter half-lives, such as clonazepam, may be effective in treating tinnitus, but their long-term use must be carefully monitored (KIM SH, et al., 2021).

Anticonvulsants treat tinnitus by enhancing GABA activity, reducing glutamate levels, and blocking sodium channels. Carbamazepine and gabapentin may be effective, but placebo-controlled studies are inconclusive. Sodium valproate is less effective than carbamazepine. Phenytoin sodium's efficacy remains unclear, with contradictory results. It may benefit patients who respond to carbamazepine but experience adverse effects.

Dosage should be increased gradually up to 100 mg/day, with monitoring of blood and leukocyte concentrations (KIM SH, et al., 2021).

In an RCT by Mahmoodi et al. (2017), 70 tinnitus patients were assigned to two groups: melatonin (3 mg/day) and sertraline (50 mg/day). Both treatments were administered for 3 months. The THI questionnaire measured tinnitus severity pre- and post-treatment. Melatonin and sertraline were both effective in treating tinnitus, with melatonin (3 mg/day) showing greater effectiveness. Initial THI scores for melatonin and sertraline groups were 45.02 ± 17.67 and 44.85 ± 20.57 , respectively. After 3 months, THI scores significantly decreased for melatonin (30.29 ± 19.62) and sertraline (36.96 ± 25.03) groups ($P < 0.01$, both). Melatonin (3 mg/day) demonstrated a significant decrease in THI scores ($P = 0.02$), highlighting its superior efficacy compared to sertraline in managing tinnitus symptoms.

Non Pharmacological Treatments for Tinnitus: Cognitive Behavioral Therapy

CBT shows promise in treating chronic subjective tinnitus, addressing cognitive and behavioral issues. A study of 100 patients randomly allocated into control and intervention groups found that CBT combined with masking therapy and sound treatment was more effective than control, improving psychological factors, tinnitus measures, and modulating cortisol and interleukin-2 levels, relieving chronic tinnitus symptoms. The intervention group showed decreased cortisol and increased interleukin-2 levels (LI J, et al., 2019). A Cochrane Review assessed 28 CBT studies conducted in Europe with 2733 participants, aged 43 to 70 years with tinnitus for at least three months, and lasting 3 to 22 weeks, and compared treatment outcomes. Compared to other interventions (*i.e.* audiological care, tinnitus retraining therapy) and versus no intervention. CBT shows promise in reducing the impact of tinnitus on quality of life and may lead to a slight reduction in depression. Adverse effects of CBT appear to be minimal or non-existent (FULLER T, et al., 2020).

One RCT compared the effectiveness of an internet-based cognitive behavioral therapy (CBT) intervention with face-to-face clinical care for treating tinnitus. It was a randomized, multicenter, noninferiority trial involving 374 adults with subjective tinnitus in the United Kingdom. Participants were assigned to receive either the internet-based intervention or standard face-to-face care. The primary outcome measure was the change in tinnitus distress assessed using the Tinnitus Functional Index (TFI). Among the 92 participants analyzed, the internet-based CBT intervention was found to be at least as effective as face-to-face care in reducing tinnitus distress. Secondary outcomes showed that the internet-based intervention was superior to face-to-face care in improving insomnia. The study suggests that internet-based CBT could be a viable alternative for individuals seeking treatment for tinnitus, providing a convenient and accessible option with comparable effectiveness to traditional face-to-face care (BEUKES EW, et al., 2018).

Tinnitus Retraining Therapy (TRT)

Tinnitus Retraining Therapy (TRT) combines sound therapy and counseling to help individuals habituate to tinnitus and reduce associated anxiety. A meta-analysis of 13 randomized controlled trials with 1345 patients showed that adding TRT to pharmacological treatment resulted in higher response rates and lower Tinnitus Handicap Inventory scores compared to medication alone. TRT with drugs proved effective in reducing tinnitus-related symptoms like anxiety and depression. However, the study lacked standardized measures and focused on a specific racial group, limiting generalizability (HAN M, et al., 2021).

One study compared CBT with TRT. In the study, three participants experienced serious adverse effects during the course of the research. One participant from the CBT group, which had a total of 22 participants, deteriorated, while two participants from the TRT group, with a total of 20 participants, also experienced deterioration. The risk ratio (RR) was calculated to assess the difference in risk between the two groups. The calculated RR value of 0.45 indicates that the risk of deterioration was lower in the CBT group compared to the TRT group. However, due to the wide confidence interval ranging from 0.04 to 4.64, there is low certainty in the precise magnitude of this difference (FULLER T, et al., 2020). A multicenter RCT conducted in 6 US military hospitals over nearly six years included 151 participants (mean age 50.6 years) with moderate to severe subjective tinnitus and adequate hearing sensitivity. They were divided into three groups: TRT (51 participants), partial TRT (51 participants), and standard of care (49 participants). The standard of care group

followed established guidelines for military healthcare, providing patient-centered counseling and treatment. Longitudinal analyses showed similar outcomes across the treatment groups, with approximately 50% experiencing significant improvements in tinnitus-related symptoms (SCHERER RW and FORMBY C, 2019).

Cochlear Implant

Cochlear implant surgery has been used for auditory rehabilitation for many years and has proven to be an important tool in improving tinnitus perception. One meta-analysis aimed to identify evidence in scientific literature indicating that cochlear implantation in patients with tinnitus can improve perception. After exclusion criteria, 6 studies, which assessed the severity of tinnitus using the Tinnitus Handicap Inventory (THI) before and after cochlear implantation, were included. The THI score was measured in 136 patients after cochlear implantation, with each patient's preoperative THI score used as a control (BORGES ALF, et al., 2021).

A statistically significant decrease in postoperative THI score was observed, indicating a reduction in tinnitus severity following cochlear implantation. The meta-analysis revealed a total reduction of 11.66 points in the THI score (95% CI 5.67 to 17.65; $p < 0.001$). However, there was significant heterogeneity among the included studies ($I^2 = 96.4\%$). The level of heterogeneity was assessed using the I^2 statistic. Given the substantial heterogeneity in the study results, a random-effects model was used to estimate mean differences, suggesting that the meta-analysis results are representative of the study population. All of the six eligible articles consistently reported improvements in tinnitus perception post cochlear implant, despite variations in the specific parameters analyzed in each study (BORGES ALF, et al., 2021).

Stapes Surgery

Otospongiosis is a genetic condition characterized by dysregulated bone resorption and formation in the temporal bone, resulting in osteodystrophy. Clinically, otospongiosis presents with progressive conductive and/or mixed hearing loss and tinnitus. The surgery involves removing the abnormal portion of the stapes bone and replacing it with a prosthesis or artificial stapes to improve sound transmission to the inner ear. A literature review found 125 articles on otosclerosis and tinnitus. Stapes surgery has traditionally focused on improving hearing, but recent research shows its potential in reducing tinnitus symptoms. Assessing tinnitus six months after surgery is optimal, with significant improvements reported. Hearing capability increased by an average of 93%, while tinnitus showed an impressive reduction of 85.52%. These findings highlight the broader benefits of stapes surgery beyond hearing improvement. However, the use of different tinnitus evaluation scales and small sample sizes limit result comparability and generalizability (CAVALCANTE AMG, et al., 2018).

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that employs magnetic fields to induce electrical currents in specific brain regions. By positioning a coil proximal to the scalp, magnetic pulses are generated and permeate the skull to elicit neuronal activation in the targeted brain area. In the context of the present study, rTMS was implemented as a therapeutic intervention for chronic tinnitus, either as a standalone treatment or in conjunction with an antidepressant medication (BILICI S, et al., 2015). In a Turkish RCT, 75 participants with moderate tinnitus underwent one-month treatment comparing repetitive transcranial magnetic stimulation (rTMS) and paroxetine. Five groups received different interventions: rTMS alone at various frequencies, rTMS with paroxetine, paroxetine alone, or a placebo. All treatment groups, except the placebo, showed improvements in tinnitus severity based on various measures. Significant improvements were observed in groups receiving rTMS alone at 1 Hz and the combined rTMS with paroxetine. Both rTMS and paroxetine have potential for reducing tinnitus severity, but their combination did not show cumulative or synergistic effects (BILICI S, et al., 2015).

Transcranial Direct Current Stimulation (tDCS)

Direct current transcranial stimulation (tDCS) is a non-invasive technique that uses a low-intensity electrical current to modulate brain activity by applying electrodes to specific scalp regions. Due to its non-invasive nature, low cost, easy application with minimal discomfort, and lower residual inhibition compared to other stimulation methods, tDCS is an interesting choice for the treatment of tinnitus. However, there is no consensus

on certain parameters for its use in this specific condition (SANTOS ADHM, et al., 2018). A systematic review of literature investigated the use of transcranial direct current stimulation (tDCS) for tinnitus treatment. Results varied depending on the electrode placement and stimulation parameters. Significant improvements in tinnitus intensity and distress were observed when the anode was positioned on the right and the cathode on the left. However, reversing the electrode positions did not yield any improvements. Other studies did not find statistically significant results in tinnitus-related scales, such as the THI and the Clinical Global Impression (CGI). Different electrode placements, including the temporoparietal area (TPA) and the dorsolateral prefrontal cortex (DLPFC), were explored. Based on this review, no therapeutic response of tinnitus to tDCS was found (SANTOS ADHM, et al., 2018).

Conversely, another systematic review examined the effects of tDCS on tinnitus symptom severity, depression, and anxiety, as well as the relationship with stimulation parameters. The results showed significant improvements in tinnitus symptoms and depression with active tDCS contrasted with placebo. Optimizing stimulation parameters and ensuring consistency in future trials are important for advancing tDCS application for tinnitus. The review also highlighted variability in electrode montage, suggesting that any montage creating a strong electric field in the frontal cortex may be effective. The optimal number of tDCS sessions was estimated at around seven, with a 20-minute session duration likely to be optimal. However, more high-quality data is needed. The analysis for anxiety did not show a significant effect, possibly due to limited data and inclusion of participants without clinical diagnoses (LABREE B, et al., 2022).

Transcranial Random Noise Stimulation (tRNS)

Transcranial random noise stimulation (tRNS) is a non-invasive brain stimulation technique using random electrical currents to modulate brain activity and enhance cognition. It delivers broad-spectrum stimulation to activate multiple neural networks simultaneously, promoting neuronal excitability and synaptic plasticity. It has been widely used in tinnitus research and gained popularity due to its superior effectiveness in reducing tinnitus symptoms with fewer side effects compared to other methods. A study examined tRNS for treating tinnitus in 29 participants. Auditory-tRNS was applied over T3 and T4, preceded by prefrontal-tRNS over F4 and FP1. One group had a single session, while the other had eight sessions. Both groups showed improvements in tinnitus intensity and annoyance. The multiple-session group had greater suppression and decreased THI scores. Auditory-tRNS was more effective than tDCS and tACS. Multiple sessions improved daily activities and sleep. tRNS was safe and well-tolerated (MOHSEN S, et al., 2020).

Acupuncture

The use of acupuncture (AC) for tinnitus treatment is described in Traditional Chinese Medicine. One RCT aimed to compare the efficacy of an AC program for tinnitus patients. Results showed that acupuncture treatment improved tinnitus perception, reduced intensity, and enhanced quality of life, contrary to most literature findings that showed no significant difference between AC and placebo. Studies with fewer than ten AC sessions may explain this disparity. Biases in participant randomization and low-quality studies were identified. Long-term effects of AC were also investigated, showing significant improvement in THI scores, sleep quality, blood circulation, and muscle relaxation. The patients demonstrated a significant improvement in tinnitus perception. Chinese scalp AC technique, combined with bilateral electroacupuncture, showed a statistically significant short-term improvement, reducing tinnitus intensity and enhancing quality of life in tinnitus patients (DOI MY, et al., 2016).

FINAL CONSIDERATIONS

Tinnitus is a prevalent and significant public health challenge that affects millions of individuals worldwide. It has a profound impact on the emotional, social, and personal well-being of those who experience it, often leading to depression, difficulty with auditory attention, headache, and sleeplessness. Effective treatment options for tinnitus are crucial in improving patients' quality of life. Pharmacological approaches, such as tricyclic antidepressants, benzodiazepines, and anticonvulsants, have shown some potential in managing tinnitus symptoms, although their efficacy remains uncertain. Non-pharmacological treatments, including

cognitive behavioral therapy, tinnitus retraining therapy, cochlear implantation, stapes surgery, and transcranial magnetic stimulation techniques, offer promising results in reducing tinnitus severity and improving patients well-being. Further research and larger-scale studies are needed to establish the effectiveness and optimal use of these treatment modalities. Developing targeted and personalized treatment plans that address the diverse manifestations and related conditions of tinnitus is essential in providing effective care to individuals suffering from this condition.

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