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What do Cochrane systematic reviews say about therapeutic tinnitus interventions?

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ABSTRACT

Introduction: Tinnitus is a sound perception not related to stimulation. It can significantly impair the quality of life and its treatment is considered one significant challenge of Medicine. **Objective:** To evaluate systematic reviews developed by Cochrane regarding therapeutic interventions for subjective tinnitus. **Methods:** It is an overview of Cochrane systematic reviews. We searched systematic reviews on Cochrane Library. The MeSH term "tinnitus" was used for searches. Inclusion criteria involved therapeutic interventions for patients with subjective tinnitus. **Results:** The search strategy recovered 577 citations with 14 Cochrane systematic reviews. 13 were included because they were focusing on primary tinnitus interventions. One review had no scope of analysis for tinnitus and it was excluded. 7,998 tinnitus patients were evaluated. **Conclusion:** There is a lack of evidence of the effectiveness of any intervention for tinnitus treatment, considering the studies performed so far and compiled in Cochrane systematic reviews.

Keywords: tinnitus; therapeutics; systematic review; evidence-based medicine.

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INTRODUCTION

Tinnitus is defined as the sensation of sound without environmental stimulation[1]. It is typically described by those who experience it as a wheezing, whistle, pressure cooker or cricket in the ears, among many other modalities of sound sensation, and is believed to be the result of abnormal neural activity at some point or points of the auditory pathway, which is erroneously interpreted by the auditory cortex as a sound stimulus. It can be objective or subjective[2]. Objective tinnitus refers to the perception of sound that can also be heard by the examiner and is usually due to turbulent blood flow or muscle contraction[3]. However, subjective tinnitus is the most prevalent and is characterized by the sound heard only by the person experiencing it[4].

Tinnitus affects between 5% and 43% of the general population and prevalence increases with age[5]. Most studies have a prevalence in the general population between 10

and 15%[6]. In São Paulo, the estimated prevalence is 22% of the population, being less frequent among women[7]. It can be experienced acutely, recovering spontaneously in minutes to weeks, but it is considered persistent and unlikely to resolve spontaneously when experienced for more than six months[8,9].

For many people, tinnitus is persistent and problematic and has disabling effects such as insomnia, difficulty concentrating, communication difficulties and social interaction, and negative emotional responses such as anxiety and depression. Nevertheless, suicidal ideation is present in some cases[10]. In about 70% of cases[11], persistent subjective tinnitus is associated with some degree of hearing loss[10]. However, the association between hearing loss and tinnitus is not simple or direct and not all people with hearing loss experience tinnitus and, conversely, some people with clinically normal hearing have tinnitus[12].

Considering the pathophysiology of tinnitus, different theories involve changes in the function or activity of the peripheral (cochlea and auditory nerve) or central auditory systems[13]. Of those related to the peripheral system, the most accepted is the theory of disproportionate damage: there is loss of function of outer hair cells (OHC) but inner hair cells (IHC) are preserved, inducing hyperactivity of IHC by the reduced inhibitory activity of OHC. Aberrant depolarizing activity may also have a biochemical basis, resulting from excitotoxicity or stress-induced increase in glutamate release of IHC with positive regulation of N-methyl-D-aspartate (NMDA) receptors[14-16].

Several other theories seek to explain the pathophysiology of tinnitus, but the fact is that this symptom remains a cause of discomfort for those who feel it and a challenge for physicians, who have difficulty treating it effectively[2].

This study aimed to sum up the evidence of systematic reviews of the Cochrane Collaboration, regarding the efficacy of therapeutic interventions for subjective tinnitus.

METHODS

Study Design

This is an overview of systematic reviews published in the Cochrane Library. There were no restrictions on the location, date and language in which the studies were published.

Inclusion criteria

Types of participants: All systematic reviews involving randomized clinical trials with primary therapeutic interventions for subjective tinnitus and which are in the Cochrane Library database.

Types of interventions: therapeutic procedures involving tinnitus compared to placebo, or any other drug or non-drug intervention.

Types of results: any results (clinical improvement, improvement in quality of life, adverse events, etc.) found in the studies were considered.

Process of search and selection of studies

The search for systematic reviews was carried out on January 3, 2021, using the official terminology of the Medical Heading Subjects (MeSH) and the Cochrane Library via Wiley. The search strategy was carried out using the term: "tinnitus". The analyses of the studies, as well as the extraction of the data, were carried out respecting the described inclusion criteria.

All revisions found were analyzed from the full text. Data were extracted from the original files of systematic reviews.

A predetermined extraction sheet was used, it contained the following main points: year of publication, authors' name and title of the review, number of primary studies, types and number of participants, interventions and results, analysis of bias and their justifications, details of intervention groups, duration and parameters, follow-up period and, when present, statistical values in meta-analysis, relative risk format, differences between standardized or non-standardized means and confidence interval.

The quantitative analyses used of the continuous variables were grouped into mean difference or standardized mean difference with a 95% confidence interval.

RESULTS

The search strategy retrieved in January 2021 a total of 577 citations in the Cochrane Library. Of the total, 563 were clinical trials and 14 were systematic reviews. Of these, one did not relate to the topic of tinnitus as the primary endpoint of analysis. Thirteen systematic reviews were included.

The main characteristics of the studies included[17-29] are presented in Table 1. The effects of the interventions are presented in Table 2.

DISCUSSION

Tinnitus is considered a symptom of difficult control in the literature and is a challenge for otorhinolaryngologists[2]. For decades considered as incurable, it is noted in specialized outpatient clinics that some patients have a very satisfactory response to treatment, but without a ready prescription for all patients can be pointed out [30].

This study corroborates this context. No intervention has shown effectiveness so far in the systematic reviews performed by Cochrane. Even ginkgo biloba extract, so prescribed for tinnitus and established media target, showed no efficacy for tinnitus[21].

Table 1: Main characteristics of the studies included.

Author/Year	Sample	Intervention	Risk of bias	Conclusion
Hall et al. 2018[17]	5 RCTs - n=303	Betaistine	uncertain	No evidence
Sereda et al. 2018[18]	8 RCTs - n=590	Sound therapy with amplification or sound generator	uncertain	No evidence
Person et al. 2016[19]	3 RCTs - n=209	Zinc	moderate to high	No evidence
Hoare et al. 2014[20]	1 RCT - n=91	Individual Sound Amplification Device	low to uncertain	No evidence
Hilton et al. 2013[21]	4 RCTs - n=1543	Ginkgo biloba extract	low	No evidence
Baldo et al. 2012[22]	6 RCTs - n=610	Antidepressants	high	No evidence
Bennett et al. 2012[23]	7 RCTs - n=392	Hyperbaric oxygen therapy	moderate	No evidence
Hobson et al. 2012[24]	5 RCTs - n=553	Sound therapy (masking)	moderate to high	No evidence
Hoekstra et al. 2011[25]	7 RCTs - n=453	Anticonvulsants	high to uncertain	Limited evidence - small effect (clinically dubious)
Meng et al. 2011[26]	5 RCTs - n=233	Transcranial magnetic stimulation (TMS)	low	Limited evidence - favorable to TMS
Martinez-Devesa et al. 2010[27]	8 RCTs - n=468	Cognitive-behavioral therapy	low to uncertain	(1) lack of evidence for tinnitus improvement (2) Improvement of depression (3) Improvement in quality of life
Phillips et al. 2010[28]	1 RCT - n=123	Tinnitus retraining therapy (TRT)	high	Limited evidence - favorable to TRT
Fuller et a. 2020[29]	28 RCTs - n=2733	Cognitive-behavioral therapy	low to moderate	Limited evidence (1) Improvement in quality of life between 6-12 months of treatment

RCT: Randomized Clinical Trial

Table 2: Effects of interventions.

Author/Year	Intervention	Statistics (primary outcome - tinnitus improvement)	Serious Adverse Events
Hall et al. 2018[17]	Betaistine	DM: -0.16, 95% CI -1.01 to 0.70 (visual analog scale)	No
Sereda et al. 2018[18]	Sound therapy with amplification or sound generator	DM:-0.15, 95% CI -0.52 to 0.22 (THI questionnaire)	No
Person et al. 2016[19]	Zinc	RR: 2.53, 95% CI 0.50-12.70 (THI questionnaire)	No
Hoare et al. 2014[20]	Individual Sound Amplification Device	DM:-0.90, 95% CI -7.92 to 6.12 (THI questionnaire)	No
Hilton et al. 2014[21]	Ginkgo biloba extract	*	No
Baldo et al. 2014[22]	Antidepressants	*	No
Bennett et al. 2012[23]	Hyperbaric oxygen therapy	*	No
Hobson et al. 2012[24]	Sound therapy (masking)	*	No
Hoekstra et al. 2011[25]	Anticonvulsants	RD=14%, 95% CI 6% to 22% (THI questionnaire)	No
Meng et al. 2011[26]	Transcranial magnetic stimulation (TMS)	RR:4.17, 95% IC 1.30 to 13.40 (THI questionnaire)	No
Martinez-Devesa et al. 2010[27]	Cognitive-behavioral therapy	*	No
Phillips et al. 2010[28]	Tinnitus retraining therapy (TRT)	**	No
Fuller et a. 2020[29]	Cognitive-behavioral therapy	- *versus* hearing care (counseling) - THI (DM) -5.65, 95% CI -9.79 to -1.50, 3 studies (n=444); - *versus* TRT - THI (MD) -15.79, 95% CI -27.91 to 3.67, 1 study (n=42) - *versus* active control (relaxation, internet forums etc) - THI (SMD) -0.30, 95% CI 0.55 to -0.05, 12 studies (n=966); - *versus* no intervention - THI (SMD) -0.56, 95% CI -0.83 to -0.30, 14 study (n=537)	No

DM: Difference of Means; RD: Risk Difference; CI: Confidence Interval; RR: Relative Risk; THI: Tinnitus Handicap Inventory.
*Statistic not performed due to differences between the studies evaluated; **single study included.

In addition to ginkgo biloba extract, the other drug interventions evaluated by Cochrane (betaistine, zinc and antidepressants) also did not show effectiveness in the treatment of tinnitus. Treatment with anticonvulsants showed very limited but clinically dubious evidence. Non-drug interventions (masking, hearing aids, sound therapy, hyperbaric therapy and cognitive-behavioral therapy) were also not effective. However, tinnitus retraining therapy (TRT) and transcranial magnetic stimulation showed limited evidence regarding tinnitus improvement.

However, the subject is far from exhaustion. Numerous points should be considered and some are essential for understanding: (1) the heterogeneity in the inclusion and analysis parameters in clinical trials conducted so far, (2) the lack of standardization of questionnaires for the evaluation of outcomes in these studies, since it is a subjective symptom and, therefore, exposed to many variables, (3) the low quality of studies, which exposes the high risk of bias and (4) the low number of participants in the studies conducted so far, among others.

On the other hand, the interventions performed and evaluated by Cochrane have not identified relevant adverse events to date. The effectiveness of the evaluated therapies could not be supported so far.

The drug treatment of tinnitus is the most described in the literature, but non-drug interventions have been gaining strength, especially since this millennium[30]. In all scenarios analyzed in Cochrane systematic reviews, there is an emphasis on the low number of participants in the included studies, which considerably limits any definitive conclusions. The search for the best evidence should be continued.

There are many pathophysiological mechanisms related to tinnitus and certainly many others still unknown. Full knowledge of the pathophysiology of tinnitus is considered a fundamental foundation in the scope of its treatment[30].

There are around 300 conditions that may be associated with the genesis of tinnitus. Of course, it is a mandatory role to correlate the symptom to the underlying disease as much as possible, treating this and, consequently, the attempt to reduce the impact of the sound sensation that torments the patient[19].

In the 1990s, Jastreboff[31] described that tinnitus begins in the auditory system, especially in the cochlea, but that it undergoes modifications in the central nervous system, mainly by the imposing action of the limbic system, as it proceeds to the subcortical areas.

In the context, tinnitus could have distinct connotation among people: while ones could get used to the symptom, a condition in which tinnitus bothers little or nothing, another would have intense suffering by the summation effect imposed by the limbic system, being this condition precipitated by negative feelings, tension and anguish[30,31]. The neurophysiological model thus manages to explain the differences in clinical responses to the same proposed treatment and warns that the subjective condition of the symptom must be considered in the diagnostic investigation process.

These aspects correlate with the clinical evaluation of patients with tinnitus, recommending the use of symptom self-assessment questionnaires. The Tinnitus Handicap Inventory (THI) has been the most used in practice and is a good predictor of patients with a high degree of anxiety and depression, assisting in the diagnostic amplitude and consequent global therapeutic approach, which should always be individualized[19]. The lack of use of standardized questionnaires in primary studies was an important limitation in clinical trials that served as the basis for Cochrane systematic reviews related to the investigation of therapeutic interventions for tinnitus.

It is also permissible to consider that tinnitus is exposed in multiple scenarios, and the allocation of symptomatic patients in subgroups that allow greater homogeneity, such as patients without dysacusis and patients with cochleopathy and complaints of hypoacusis or presence/absence of signs of limbic recruitment is the most appropriate.

Scientific research, especially in the last two decades, suggests that the pathophysiology of tinnitus may involve multiple key points in the chain of events evoked from the cochlear-level symptom trigger. Thus, the sensation of tinnitus can differ dramatically among those affected, even starting from the same cause, or generating source. This information presupposes that the participation of patients with tinnitus in clinical studies follows standardized inclusion parameters under the contemporary light of how science understands the symptom. Undoubtedly, in this context, the researcher should be aligned with these concepts, and should apply them with conceptual and methodological rigor aiming to clarify therapeutic mechanisms that are effective in the treatment of tinnitus and this symptom is no longer so villainous for patients and physicians.

Conclusion

There is no evidence, to date, of the effectiveness of any intervention, drug or not, for the treatment of tinnitus, with regard to the studies conducted and compiled in Cochrane systematic reviews. It is noteworthy that the studies conducted are quite heterogeneous and with a low number of participants. In this context, it is suggested that new clinical trials be conducted and parameterization in the methodology and analysis of the closures linked to tinnitus.

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