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Effectiveness of Current Pharmacotherapy Treatments for Tinnitus: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 August 2024 and was last updated on 14 August 2024.

INTRODUCTION

Review question / Objective This study aims to compare the outcomes of different pharmacotherapies in treating tinnitus using a comprehensive network meta-analysis, with tinnitus handicap inventory (THI) as the primary outcome, and annoyance and tinnitus loudness as secondary outcomes.

Condition being studied Tinnitus, a prevalent audiological condition, is characterized by the perception of a ringing or buzzing sound in the absence of a corresponding auditory source. It can result from various factors, including aging, noise, ototoxicity drugs, head and neck trauma. While the exact processes driving tinnitus remain incompletely comprehended, abnormal neural activity and connectivity in both auditory and non-auditory pathways might play a vital role. Tinnitus can significantly impact patients' quality of life, causing sleep disturbances, concentration difficulties, and emotional distress.

METHODS

Search strategy We conducted electronic searches in PubMed, EMBASE, Cochrane, and CINAHL databases from January 2000 inception until December 2023.

Participant or population Patients with tinnitus.

Intervention Pharmaceutical therapies.

Comparator Other pharmaceutical therapies or placebo.

Study designs to be included Randomized controlled trial.

Eligibility criteria (P) Population: adults with tinnitus including idiopathic subjective non-pulsative tinnitus, acute and chronic tinnitus; those focused on tinnitus with noise-induced or trauma-induced sudden hearing loss or deafness, vestibular disorders were excluded (I) Intervention: pharmaceutical treatments; (C) Comparator: other

drug treatments or placebo; (O) Outcomes: the primary outcome is the change in pre- to post-treatment tinnitus handicap inventory (THI); the secondary outcomes include the change in annoyance and tinnitus loudness; and (S) Study type: RCTs; conference abstracts, open-label studies were excluded for the data completeness and blindness bias.

Information sources Four electronic databases.

Main outcome(s) Outcomes: the primary outcome is the change in pre- to post-treatment tinnitus handicap inventory (THI); the secondary outcomes include the changes in annoyance and tinnitus loudness.

Quality assessment / Risk of bias analysis Two reviewers independently evaluated the risk of bias (ROB) in RCTs following the guidelines outlined in the Cochrane Handbook. The assessment considered the following six domains: (i) selection bias, (ii) performance bias, (iii) detection bias (iv) attrition bias, (v) reporting bias, and (vi) other bias. Each domain was rated on a scale of 0 (low risk of bias), 1 (unclear risk of bias), or 2 (high risk of bias). The overall quality of the study was determined based on the cumulative scores, with a score of 0-1 indicating high quality, 2-3 indicating moderate quality, and >3 indicating low quality.
The researchers evaluated the certainty of the evidence for the outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The quality of evidence was categorized as high, moderate, low, or very low based on specific criteria including study limitations, inconsistency, indirectness, imprecision, and publication bias.

Strategy of data synthesis Network meta-analyses were conducted to compare different pharmaceutical treatment strategies by the R software (version 4.1.3) using the following packages: “gemtc”, “rjags”, “dmetar”, “ggplot2”, and “BUGSnet”. For each outcome, network plots were firstly generated to visualize the network, with interventions represented as nodes and node size indicating the corresponding patient number. The edges on the plots represent the number of studies. Then, the results were evaluated by calculating the pooled estimates of risk ratio for dichotomous outcomes or standardized mean differences (SMD) for continuous outcomes with 95% confidence interval (CI), which makes the different results with different scales and questionnaires comparable. The decreased values of outcomes were recorded for the analysis. Both random and fixed effect models were generated and the goodness fit of each model was assessed through leverage plots that display the posterior mean of the residual deviance (Dres), the effective number of parameters which is calculated as the sum of the leverages (pD), and deviance information criterion (DIC). According to a visual examination of the leverage plots and comparison of these parameters, the model with fewer outliers and smaller parameter values would be preferred. The authors used the Markov Chain Monte Carlo algorithm for every eligible outcome and based on 100,000 simulation iterations and 20,000 adaptation iterations. A thinning interval of 10 was applied, which collected 1 sample every 10 iterations. We evaluated consistency statistically using node-splitting analysis that illustrates the inconsistency between indirect and direct comparisons 24. The residual heterogeneity and inconsistency were also calculated. League plot was created showing the SMD and CI for all treatment contrasts facilitating direct and indirect pairwise comparisons. Treatments were further ranked using the surface under the curve cumulative ranking probabilities (SUCRA). Subgroup analysis was also conducted for further exploration. Statistical significance was determined using a p-value threshold of 0.05. All analyses and visualizations were performed by the R software (version 4.1.3).

Subgroup analysis Subgroup analysis will be conducted based on the type of tinnitus: chronic or acute.

Sensitivity analysis The sensitivity analysis will be conducted if there is any significant bias among the included RCTs.

Language restriction None.

Country(ies) involved China.

Keywords Tinnitus, Pharmacological intervention, Systematic review, Meta-analysis.

Contributions of each author
Author 1 - Peifan Li - Author 1 drafted the manuscript, collected and analyzed the data, and completed the visualization.
Author 2 - Chenhao Che - Author 2 collected the data, drafted the manuscript, and helped to perform the bias assessment.
Author 3 - Yongzhen Wu - Author 3 validated the results and helped to perform the bias assessment.
Author 4 - Shan Sun - Author 4 supervised the study and acquired the funding.