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Pharmacotherapy Options for the Management of Subjective 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 23 March 2025.

INTRODUCTION

Review question / Objective We aim to conduct a comprehensive systematic review and evaluation of pharmacotherapies for subjective tinnitus using randomized controlled trials (RCTs).

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 a comprehensive search across four electronic databases: PubMed, EMBASE, Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete from interception to March 6, 2025 without language restriction.

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 severity of the tinnitus; 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 PubMed, EMBASE, Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete.

Main outcome(s) The primary outcome is the change in severity of the tinnitus.

Additional outcome(s) The secondary outcomes include the change in annoyance and tinnitus loudness.

Data management Two authors (P.F.L. and C.H.C.) independently retrieved and screened full articles based on the selection criteria. Any discrepancies were first attempted to resolve through discussion and consensus in a meeting between the two authors. If consensus could not be reached through discussion, a third senior reviewer (S.S.) was consulted to provide an independent assessment and help resolve the disagreement. The third reviewer's decision was considered final and binding to ensure consistency and objectivity in the review process. For the studies written in languages other than English or Chinese, we implemented a comprehensive translation protocol. Non-English studies were translated into English by qualified translators who possessed specialized knowledge in the subject area. The translation accuracy was further ensured by having a second independent translator cross-check and validate the translated content. Any discrepancies were discussed between the two translators and the senior scholar (S.S.). Data extraction was performed using a standardized and pre-piloted Excel form. The following information was recorded under specific headings: author, year of publication, study design, tinnitus details including tinnitus type, duration, patient age, pharmaceutical interventions, sample size, route, follow-up duration, and outcomes.

Quality assessment / Risk of bias analysis Two reviewers (P.F.L. and C.H.C.) independently evaluated the risk of bias (ROB) in RCTs following the guidelines outlined in the Cochrane Handbook using the ROB2 excel tool. The assessment considered following five domains: (i) selection bias, (ii) performance bias, (iii) detection bias (iv) attrition bias, (v) reporting bias. Each domain was rated on a scale of low risk of bias, some concern, or high risk of bias. The overall quality of the study was determined following the Cochrane handbook: low ROB if all domains are low ROB; some concerns if at least one domain some concern but no high ROB for any domain; high ROB in at least one high ROB domain.

The quality of evidence for each outcome is assessed following the GRADE handbook and determined independently by 2 investigators (P.F.L. and C.C.C.), which consists the following criteria: 1) Risk of Bias: Evaluating the methodological quality of studies; 2) Inconsistency: Assessing the variability of results across studies; 3) Indirectness: Determining if the evidence applies to the population, intervention, comparator, or outcome of interest; 4) Imprecision: Evaluating the width of confidence intervals and the sample size; 5) Publication Bias: Considering whether there is evidence of selective reporting or missing studies. Evidence from randomized controlled trials starts as high-quality (represented by ⊕⊕⊕⊕) but can be downgraded based on the above factors (moderate ◯⊕⊕⊕, low ◯◯⊕⊕, or very low ◯◯◯⊕). In case of any disparities during the ROB and GRADE assessment process, the two investigators would first discuss and turn to the senior investigator (S.S.) if opinions are not aligned.

Strategy of data synthesis Network meta-analyses were conducted to compare different pharmaceutical treatment strategies by the R software (version 4.1.3). For each outcome, network plots were first 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.

The authors used the frequentist network meta-analysis with R package "netmeta". Fixed effect model was first assessed for heterogeneity in the network metanalysis and adopted when I2 values < 50. When I2 values $\geq 50\%$ as heterogeneity indicated, the random effect model was chosen. Other statistical parameters of heterogeneity

(within treatment contrasts) and inconsistency (between treatment contrasts) such as tau2 and Q values were also documented. Further, we evaluated the detail inconsistency between indirect and direct comparisons using node-splitting analysis. League table 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) and the treatment effect was illustrated with forest plots compared with placebo. To assess the publication bias in the meta-analysis, we employed comparison adjusted funnel plots and Egger regression.

Subgroup analysis For subgroup analyses, we will examine the effect size for primary outcome across predefined subgroups based on chronic tinnitus, ROB, measurement scales.

Sensitivity analysis For sensitivity analyses, we systematically evaluated the robustness of our meta-analysis results by assessing the impact of excluding each study (leave one out) and the per protocol results.

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.