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A Systematic Review of Eligibility and Outcomes in Tinnitus Trials: Reassessment of Tinnitus Guideline

Colleen T. Plein, MD[1], Jonathan Harounian, MD[1], Elizabeth Floyd, MD[1], Rachel Irizarry, MD[1], George Ferzli, MD[1], Sarah Kidwai, MD[2], and Richard M. Rosenfeld, MD, MPH[1]

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Abstract

Objective. To analyze existing tinnitus treatment trials with regard to eligibility criteria, outcome measures, study quality, and external validity and to recognize the effect of patient demographics, symptom duration, severity, and otologic comorbidity on research findings to help practitioners apply them to patient encounters.

Data Sources. Systematic literature search conducted by an information specialist for development of the American Academy of Otolaryngology—Head and Neck Surgery Foundation's tinnitus clinical practice guideline.

Review Methods. Articles were assessed for eligibility with the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and data extracted by 2 independent investigators. Studies were assessed for methodological quality, inclusion and exclusion criteria, patient demographics, and outcome measures.

Results. A total of 147 randomized trials met inclusion criteria. Nearly all studies took place in a specialist setting. More than 50% did not explicitly define tinnitus, and 44% used a subjective severity threshold, such as "severely disturbing." Fifty-four percent required symptom duration of at least 6 months for study eligibility, and up to 33% excluded patients with "organic" hearing loss or otologic conditions. Mean age was 52.2 years, and median follow-up was 3 months. Only 20% had a low risk of bias.

Conclusion. Randomized trials of tinnitus interventions are most applicable to older adults with tinnitus lasting $\geq$6 months who are evaluated in specialty settings. High risk of bias, short follow-up, and outcome reporting raise concerns about the validity of findings and may influence how clinicians apply trial results to individual patients and establish treatment expectations, thus demonstrating the need for further quality research in this field.

Keywords

tinnitus, clinical practice guideline, systematic review, external validity, outcome measures

Tinnitus, or the perception of a sound without an external source, has an estimated prevalence of approximately 10% to 15% in the US population,[1] with about 20% of those affected seeking clinical intervention.[2] It is a frequent, troublesome complaint of patients presenting to otolaryngologists, primary care providers, and other clinicians, including audiologists and psychologists.

Much research has been devoted to managing tinnitus, including a recent clinical practice guideline published by the American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF).[3] Many of the guideline recommendations are based on randomized controlled trials (RCTs) or systematic reviews of RCTs, which contain diverse participants with varying degrees of tinnitus duration and severity. The guideline authors defined their target patient as one with tinnitus that is ''bothersome and persistent (lasting 6 months or longer),'' based on group consensus and a rough estimate of the ''typical'' patient included in tinnitus trials. The validity of this assumption, however, is unknown and could affect the external validity (generalizability) of the guideline because not all RCTs included in the guideline had similar subject selection criteria.[4]

The aim of this study was to help clinicians better identify which patients with tinnitus are most similar to those enrolled in RCTs, thereby increasing the chances that outcomes achieved in those same studies could be expected in their own patients. We sought to analyze the tinnitus RCTs used to formulate recommendations in the AAO-HNSF

[1]Department of Otolaryngology, SUNY Downstate Medical Center, Brooklyn, New York, USA
[2]Icahn School of Medicine at Mount Sinai, New York, New York, USA

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Corresponding Author:
Colleen T. Plein, MD, Department of Otolaryngology, SUNY Downstate Medical Center, 450 Clarkson Ave, Brooklyn, NY 11203, USA.
Email: colleen.plein@downstate.edu

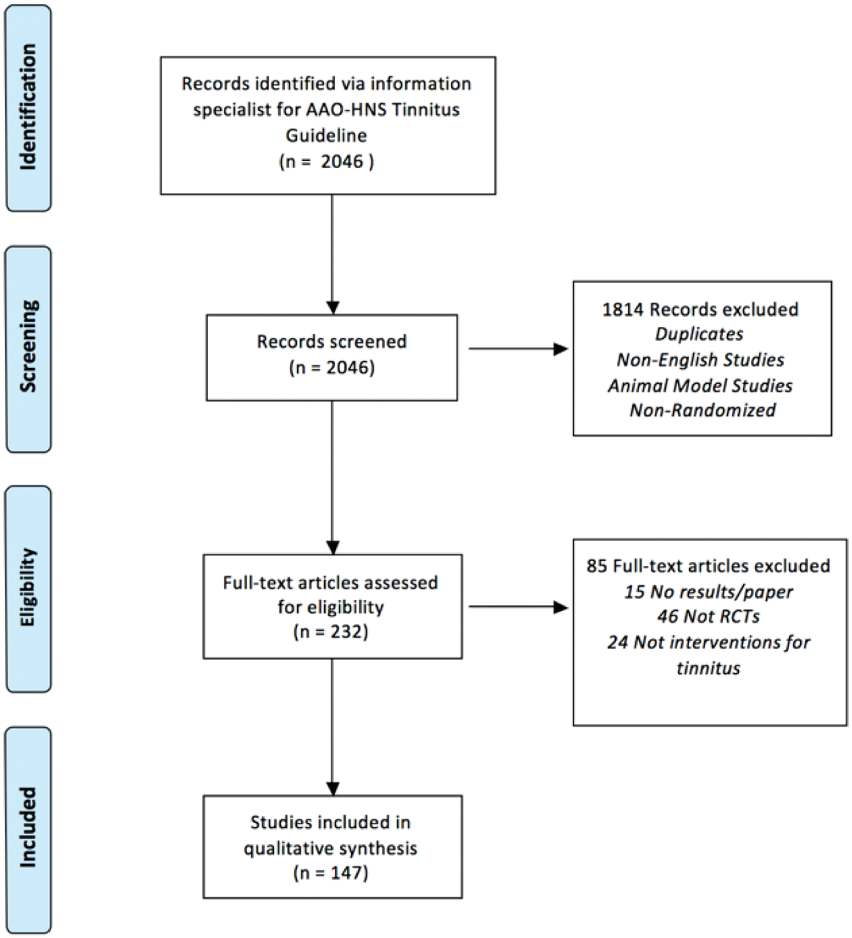

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram describing article selection and inclusion. AAO-HNSF, American Academy of Otolaryngology—Head and Neck Surgery Foundation; RCT, randomized controlled trial.

clinical practice guideline[3] with regard to patient demographics, eligibility criteria, outcome measures, and study quality. Our goal was to assess the external validity of the existing trials and to better understand how the results of individual RCTs and systematic reviews may apply to individual patient encounters.

Methods

Literature Search

We relied on the systematic literature search conducted by an information specialist to identify RCTs of tinnitus treatment for use in developing the AAO-HNSF tinnitus clinical practice guideline.[3] The search included all trials identified through March 12, 2013. A full description of the search methodology is outlined in the published guideline.[3]

Study Selection

Study selection was performed in accordance with the PRISMA protocol[4] (Preferred Reporting Items for Systematic Reviews and Meta-analyses; **Figure 1**). The initial literature search yielded 2046 studies for abstracts screening, of which 1814 studies were excluded as duplicates, non-English papers, animal model studies, or nonrandomized trials. The remaining 232 full-text studies were screened by 2 independent reviewers (C.T.P. and E.F.) for 3 inclusion criteria: $\geq$2 independent patient groups treated differently, randomization of patients, and reporting of tinnitus outcomes (if the study examined symptoms other than tinnitus, tinnitus results were reported separately). This yielded 147 studies (**Figure 1**) for inclusion in data abstraction and analysis.[5-151]

Data Abstraction

A data abstraction form was developed to standardize data collection. All data abstractors underwent training on a common set of 5 studies to ensure consistent data collection among different reviewers. Each included study was abstracted by 2 independent reviewers, with any discrepancies reviewed and resolved by the senior author (C.T.P.). Included studies were assessed for patient demographics, treatment setting (specialty vs primary care), and funding sources. Of particular interest was a stated definition of tinnitus and the details of specific inclusion and exclusion criteria, including symptom duration, frequency, and quality, as well as any comorbid conditions. The use of validated instruments for assessing tinnitus symptoms was included, as was the use of any audiometric

Table 1. Description of Randomized Controlled Trials.

	%[a]
Publication year, median	2007[b]
Intervention type	
Drug	44
Device	27
Behavioral	22
Other (CAM, HBOT)	7
Geographic location	
Europe	59
North America	16
Asia	14
South America	7
Oceana	2.7
Africa	1.4
Funding source	
Unfunded	48
Nonindustry	37
Industry	8
Both	7

Abbreviations: CAM, complementary and alternative medicine; HBOT, hyperbaric oxygen therapy.
[a]In percentages, except for publication year.
[b]First quartile, 1999; third quartile, 2011; interquartile range, 12.

data. Data were obtained regarding treatment type and duration, patient compliance, length of follow-up, and adverse event reporting.

Quality Assessment

All included studies were assessed for risk of bias with the Jadad criteria[152]: method of randomization (if stated), blinding, withdrawal and dropout rates, and analysis of data on intent-to-treat basis. With this scale, a score of 5 would indicate the lowest risk of bias, and a score of 1 would indicate the highest risk.

Results

Study Characteristics

Nearly all studies took place in a specialist setting. The most common geographic location was Europe (59%), followed by North America (16%), Asia (14%), and South America (7%; **Table 1**). Mean publication year was 2007 (first quartile, 1999; third quartile, 2011; interquartile range, 12). Intervention type included drugs (44%), devices (27%), and behavioral treatment (22%), with the remainder (7%) mostly consisting of hyperbaric oxygen therapy or complementary and alternative therapies. Eight percent of studies were industry funded, compared with 37% that had nonindustry funding and 48% that were unfunded or did not report funding sources.

Risk of Bias

Thirty studies (20%) had a low risk of bias, defined as having all 3 of the following: randomization method specified, randomization method adequate, and double blinding (**Table 2**). Studies with low risk of bias had a median publication year of 2011, compared with 2006 for all others ($P < .001$, Mann-Whitney U test).

Table 2. Quality Assessment of Studies.

	%
Randomization method specified	
Yes	45
No	55
Adequate randomization	
Yes	45
No	55
Double blind	
Yes	48
No	52
Withdrawals/dropouts specified	
Yes	76
No	24
Intent-to-treat analysis	
Yes	44
No	56

Table 3. Description of Subjects.

	Values
Sample size, median, n	55[a]
Age, mean ± SD, y	52.2 ± 7.2[b]
Most common minimum age, y	18 (30%)
Most common maximum age, y	65 (8%)
Adults only	77%
Included children (≤16 y)	5%
Sex: male	62%[c]

[a]Range, 4-800; first quartile, 35; third quartile, 80; interquartile range, 45.
[b]Range, 16-85 years.
[c]Range, 21%-79%.

Patient Demographics

Median sample size was 55, with a range of 4 to 800 (first quartile, 35; third quartile, 80; interquartile range, 45; **Table 3**). Only 5% of studies included children, and 77% included adults only. Mean patient age was 52.2 ± 7.2 years, with a range of 16 to 85, although the most common upper and lower age limits for inclusion were 18 and 65. The majority of patients were male (mean, 62%; range, 21%-79%).

Description of Tinnitus

A definition of tinnitus was stated in 65 studies (44%), most often some type of subjective perception, ranging from ''awareness'' to ''severely disturbing'' (**Table 4**). Only 10% specified a frequency of symptoms, most often ''constant,'' and 11% specified a quality of the tinnitus, most often ''nonpulsatile.''

Table 4. Description of Tinnitus.

	%[a]
Definition of tinnitus stated	
Yes	44
No	56
Validated tinnitus instrument used	
Yes	20
No	80
Exclusion criteria	
Retrocochlear hearing loss	33
Conductive hearing loss	31
Organic hearing loss	28
Ménière's disease	25
Traumatic hearing loss	9
Inclusion criteria: minimum symptom duration, mo	
6	28
3	11
12	9
<3	7
Audiometric measurements used	
Yes	79
No	21
Follow-up, median	3 mo[b]
Lost to follow-up, median	9[c]
Adverse events specified	42

[a]In percentages, except for median follow-up.
[b]Range, 0-24 months; first quartile, 1; third quartile, 4; interquartile range, 4.
[c]Range, 0%-85%; interquartile range, 19%.

Inclusion and Exclusion Criteria

Approximately 10% of studies required a specific frequency and quality of tinnitus symptoms for study inclusion, most often ''constant'' (7.5%) and ''nonpulsatile'' (9%). Twenty percent of studies used a score on validated tinnitus instrument, such as the Tinnitus Handicap Inventory or Tinnitus Questionnaire for inclusion (**Table 4**). Exclusion criteria included retrocochlear hearing loss (33%), conductive hearing loss (31%), ''organic hearing loss'' (typically defined as the presence of a known otologic disorder; 28%), Ménière's disease (25%), or a history of head trauma (9%). Just over half (54%) of studies specified a minimum duration of tinnitus symptoms for inclusion, most often 6 months (28%), followed by 3 months (11%). Seventy-nine percent of studies utilized some form of audiometric examination, although most commonly part of data collection rather than patient inclusion/exclusion.

Outcome Reporting

Median follow-up time was 3 months (range, 0-24; first quartile 1; third quartile, 5; interquartile range, 4; **Table 4**). A median of 9% of patients were lost to follow-up; however, 25% of studies had at least 19% of study patients lost to follow-up. Adverse events were specified in 42% of studies.

Discussion

This data analysis suggests that randomized trials of tinnitus interventions are most applicable to older adults with tinnitus lasting ≥6 months who are evaluated in specialty settings. The limitations in methodology, follow-up (50% <3 months), and outcome reporting raise concerns about the validity of findings and may influence how clinicians apply trial results to individual patients and establish treatment expectations. Concerns regarding validity should also be considered when implementing recommendations from the AAO-HNSF guideline, even though the target patient (with persistent, bothersome tinnitus for at least 6 months) is relatively similar to the ''typical'' trial patient.

This study demonstrates large heterogeneity within RCTs of interventions for tinnitus. There is a wide variation in the demographics of included patients, inclusion and exclusion criteria, as well as methods of measurement, making it particularly difficult to generalize the findings of existing research to individual patients whom clinicians may encounter in clinical settings. For example, the heterogeneity of patient demographics and description of symptoms ultimately does not allow for reliable comparisons of patients across different studies. Furthermore, the high risk of bias in most studies analyzed raises concerns about the internal validity of these studies, not to mention how these could be generalized to the typical ''tinnitus patient.'' This demonstrates a need in the literature for high-quality tinnitus research that is adequately randomized, ensures adequate follow-up, and does not exclude a large range of common otologic conditions that can result in tinnitus, which would result in improved external validity.

The published AAO-HNSF tinnitus clinical practice guideline states that ''clinicians should distinguish patients with bothersome tinnitus of recent onset from those with persistent symptoms (≥6 months).''[3] While 6 months was the most common specified duration of symptoms in the analyzed trials, almost half (46%) did not specify any required symptoms duration. In addition, the guideline defines bothersome tinnitus as ''that which distresses the patients and affects their quality of life and/or functional health status.'' However, less that half of the studies included in our analysis provided any definition for tinnitus, and when it was specified, it was most often subjective. Only 20% used a validated instrument to measure impacts on daily life or symptom severity.

The guideline encourages clinicians to identify underlying conditions that cause tinnitus and, if one is identified, states that the guideline no longer applies. However, only one-third of studies in this analysis excluded patients with comorbid otologic conditions that could result in tinnitus. This raises concern that it will be difficult to clinicians to properly identify patients with ''bothersome tinnitus.'' The specific standards of the published guideline mean that it may not apply to a majority of patients who may present with complaints of tinnitus. This should be addressed as the guideline is further implemented into clinical practice and updated in the future.

This study is the first to systematically review the external validity of tinnitus RCTs and has several strengths. We relied on the explicit and rigorous systematic literature search used by the AAO-HNSF in formulating its guideline as the basis for our trial selection. Our systematic review was conducted with standard methodology and was reported through PRISMA standards, with training of abstractors, eligibility assessment, and data extraction and comparison by 2 independent reviewers for all included studies. We also included a validated scale for assessing risk of bias, which is important in assessing both the reliability and generalizability of the included studies.

This study also has several limitations. The data that we sought were mainly qualitative in nature and so did not lend itself to thorough statistical analysis or meta-analysis. During the process of data collection, incongruities were reviewed and resolved by the senior author (C.T.P.). The absence of a totally independent arbiter who was not also a reviewer may have affected data collection in a minor way. In addition, we included studies published through March 2013 (as per the AAO-HNSF search), which leaves the possibility that further studies have since been published that were not included in this analysis. Although we may have introduced language bias by including only English-language studies, our intent was to assess articles included in the AAO-HNSF guideline, not the global body of tinnitus literature per se.

Using RCTs and systematic reviews of RCTs as a foundation for clinical guidance is commendable, but the importance of assessing the external validity of these analyses cannot be overstated. While they are able to give us excellent insight into what the impact of interventions may be, it is not always possible to clearly define or understand how they may be applicable across the spectrum of clinical practice. We must remember that randomized trials, including the majority of these included in our analysis, have specific and differing methods of inclusion and exclusion of patients, as well as varied risk of bias inherent in study design. Analysis of external validity is essential to the development of further guidelines and should be taken into account if we hope to develop recommendations that are of most benefit to clinicians and patients.[4]

Author Contributions

Colleen T. Plein, conception, design, acquisition, analysis and interpretation of data, drafting, critical revision of work, final approval, accountability for all aspects of the work; **Jonathan Harounian,** data acquisition analysis, drafting, final approval, accountability for all aspects of the work; **Elizabeth Floyd,** data acquisition analysis, drafting, final approval, accountability for all aspects of the work; **Rachel Irizarry,** data acquisition analysis, drafting, final approval, accountability for all aspects of the work; **George Ferzli,** data acquisition analysis, drafting, final approval, accountability for all aspects of the work; **Sarah Kidwai,** data acquisition analysis, drafting, final approval, accountability for all aspects of the work; **Richard M. Rosenfeld,** conception, design, acquisition, analysis and interpretation of data, drafting, critical revision of work, final approval, accountability for all aspects of the work.

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