The efficacy of betahistine dihydrochloride in the treatment of primary tinnitus: a randomized clinical trial study

Gustavo Leão Castilho[1], Norimar Hernandes Dias[1], and Regina Helena Garcia Martins[2]

[1]Universidade Estadual Paulista Julio de Mesquita Filho
[2]Botucatu Medical School, UNESP-Univ Estadual Paulista

July 14, 2022

Abstract

Abstract Objective: To determine whether Betahistine dihydrochloride is effective in treating primary tinnitus in adults. Design: Intention-to-treat, randomized, triple-blinding, monocentric clinical trial Setting: Botucatu Medical School – State University of São Paulo (Unesp) in Brazil. Participants: 62 adults with primary tinnitus for at least six months (both sexes), and a Tinnitus Handicap Inventory score above 18 were randomized in two equal study groups: betahistine (24 mg of oral betahistine 12/12hs for 90 days), control group (a matched placebo). Main outcomes measures: Primary outcome measure - change in Tinnitus Handicap Inventory score; secondary outcome - Clinical Global Impression Improvement and participants' perceived improvement after the intervention. Results: Participants had a median age (interquartile range) of 54 (48 to 60) years, with a balanced number of men and women. There was no significant difference in Tinnitus Handicap Inventory change before and after treatment between the study group and control (median difference of -2 points; 95% CI, -8 to 6 points); the Tinnitus Handicap Inventory after intervention was a median (interquartile range) of 4 (-4 to 14) lower in the betahistine group, and a median (interquartile range) of 2 (-6 to 10) lower in the placebo group. The secondary endpoint, covariate adjustment, and per-protocol analysis provided similar results, and side effects were without difference between both groups. Conclusion: Betahistine was ineffective when compared to the placebo in the treatment of the primary tinnitus .

Objective : to evaluate the effectiveness of betahistine in the treatment of primary tinnitus. Study Design: Clinical, randomized, placebo-controlled, triple-blind trial. Sitting: Betahistine is widely used in the treatment of tinnitus, but there is a lack of scientific evidence to prove its real effectiveness. **Methods** : Adult patients with primary tinnitus and who were not undergoing treatment for tinnitus in the last six months were included. Patients with profound sensorineural deafness, hearing aid users and patients with metabolic, neurological, psychiatric or decompensated cardiovascular diseases were excluded. Study groups: Betahistine Group, whose patients received betahistine 24 mg every 12 hours for 90 days; Control group, whose patients received placebos for 90 days. Parameters evaluated: demographic data, Tinnitus Handicap Inventory (THI), Clinical Global Impression Improvement (CGI-I) and a question of "Yes" or "No" to participants about the perception of improvement in symptoms.**Results:** Recruitment selected 284 participants, of these 62 were randomized between the 2 study groups (betahistine group n-31; Control group n-31); median age (IQ) 54 (48 to 60) years, with a balanced number of men and women. There was no difference in THI outcome after treatment between the study groups (median difference, -2 points; 95% CI, -8 to 6 points); the THI after the intervention was a median (IQ) 4 (-4 to 14) lower points in the betahistine group, and a median (IQ) 2 (-6 to 10) in the placebo group. **Conclusion** : Betahistine dihydrochloride was ineffective in the treatment of primary tinnitus in adults.

Key points

- Tinnitus is prevalent health condition without a single effective treatment.
- Betahistine is one of the most used empirical treatments for tinnitus, without reliable scientific support.

- This randomized clinical trial is the first reliable study to test betahistine use for this purpose.
- Our results reveal that this drug is ineffective for primary tinnitus in adults, therefore, its large-scale use is likely to be of no benefit to patients.
- We believe that this result can avoid the negative impact of the use of ineffective treatments by these patients.

The efficacy of betahistine dihydrochloride in the treatment of primary tinnitus: a randomized clinical trial study

Introduction

This medical condition appears almost balanced between sexes (53% female) and reports increase with aging. Tinnitus is commonly associated with hearing loss of up to 90%. Chronic tinnitus occurs when the symptom persists for longer than six months[1]. About 40% of tinnitus are idiopathic, termed 'primary tinnitus', up to 20% have disabling effects such as insomnia, anxiety, and depression and is referred to as 'bothersome tinnitus[2].

Different causes of tinnitus, such as, acoustic trauma, emotional distress, and metabolic disorders promote cochlear disfunction[1]. Postulated theories, such as discordant damage theory and maladaptive neuroplastic response theory, predict that the cochlear disfunction reduces cochlear nerve inhibition, resulting in hyperexcitability of the auditory neural center perceived as tinnitus[3]. There is no standard treatment across a wide range of interventions, such as transcranial magnetic stimulation, sounds, and cognitive-behavioral therapies; moreover, many of them are difficult to access[4, 5].

Betahistine dihydrochloride was initially indicated for Ménière's disease, but its empirical use for primary tinnitus has progressively increased in several countrie[6]. For instance, in the United Kingdom it was the most prescribed tinnitus medication by otolaryngologists and the second by general practitioners[7]. The drug is a weak histamine H1 receptor agonist and a potent histamine H3 receptor antagonist.[3] It is believed to improve cochlear blood flow[8] and neural function,[9]diminishing the effects of cochlear disfunction and central auditory hyperactivity.

This is encouraged by promising scientific results (32.8% of clinical improvement vs. 17.0% untreated);[10,11] safety (similar to the placebo);[3] and accessibility even in emerging countries (e.g., one month of treatment cost about 5.0% of the Brazilian minimal wage). However, in a recent systematic review by Wegner et al.[3], only five clinical trials were selected, all of which were compromised by methodologic flaws.

Objective

This clinical trial aims to evaluate the efficacy of betahistine dihydrochloride in the treatment of primary tinnitus in adults.

Methods

Ethical considerations

This study was approved by the Research Ethics Committee of our institution (process number XXXX) and registered at ensaiosclinicos.gov.br (identifier: XXX). All participants signed the consent form. The pharmaceutical company Eurofarma S.A. donated the interventional drug and placebo and provided external support staff to centralize randomization. Its company were not involved in study design, intervention control, data management, or the manuscript.

Study Design and participants

This study reports a monocentric, randomized, triple-blind, placebo-controlled, parallel-group trial, following the SPIRIT guideline and CONSORT statement, and was performed between November 1, 2018, and July 4, 2021. Clinical evaluation and visits were performed at the Institutional Clinical Research Center of our Hospital, and examinations at the Institutional Otorhinolaryngology Service and Laboratory. The initial and follow-up visits were scheduled before and after the intervention, on days 0 and 90, respectively. Participants

were contacted an additional three times by phone during the treatment, on days 15, 45, and 75, to ensure adherence and monitor adverse events.

The Tinnitus Research Initiative case history questionary, audiometry (Interacoustics, model AC40 with phone model TDH 39, Middelfart, Denmark), immittance testing (Madsen, model Zodiac 901, Copenhagen, Denmark), otolaryngology examination, magnetic resonance exam (when retrocochlear pathology was suspected),[12] and laboratory tests were performed during the participants' eligibility evaluation.

Qualified participants were further evaluated to recheck their baseline characteristics and to measure the first Tinnitus Handicap Inventory score (THI) – primary endpoint (initial visit). The final THI and secondary endpoints were measured in the follow-up visit. The principal investigator managed these visits; no other investigators were involved. Adverse events and adherence were monitored by a pharmacist. Future treatment was guaranteed for the placebo group in case of proof of drug efficacy.

Participants were recruited between November 2018 and March 2020 using social media, and radio as well as a healthcare provider-based clinical invitation. No financial compensation was offered. Adult participants aged 18 to 70 years with non-pulsatile tinnitus for at least six months of both sexes, and a THI score superior or equal to 18 before randomization were eligible.

Exclusion criteria were: middle ear disease; moderate hearing loss or higher; hearing aids use; hearing asymmetry or retrocochlear pathology; vestibular symptoms and Ménière's disease; incapacities to fill the THI; temporomandibular dysfunction; unstable cardiovascular, metabolic or psychiatric diseases; neurodegenerative, rheumatic and autoimmune diseases; pregnancy and breastfeeding; and betahistine use contra-indication. Participants were advised not to use any other treatment for tinnitus, with a wash-out period of six months.

Intervention

Participants received 24 mg of betahistine or the matching placebo every 12 hours for 90 consecutive days. This dosage was chosen because it was previously reported to generate promising results[10]and is the maximum dose recommended by health regulatory agencies in most countries[13].

Outcomes

Primary outcome. THI score[14]. The comparison of the THI score change between study groups was assessed before and after treatment. The THI consists of a 25-item questionnaire to classify participants into functional, emotional, and catastrophic subscales. Each item is scored on a Likert-scale from 0 to 4 (0 = 'no,' 2 = 'sometimes,' 4 = 'yes'), resulting in a score ranging from 0 to 100. The severity levels are considered mild between 18 and 36, moderate between 38 and 56, severe between 58 and 76, and catastrophic above 78[15]. The THI score is one of the most used scoring system to assess the effect of an intervention in tinnitus.

Secondary outcome. Participants*'* impression of improvement. These outcomes were assessed by the Clinical Global Impression of Improvement (CGI-I), which consists of a 7-point Likert scale ranging from 'very much worse' to 'very much improved'[16]and one question regarding the participant's perceived improvement resulting in a polar yes-no response. Both outcomes were measured after treatment. These outcomes were chosen to support the THI, other questionnaires were avoided so as not to compromise participants' retention.

Adverse events and adherence were also assessed in the final visit. The most common side effects of betahistine are nausea, dyspepsia, and headache[13].

Sample Size

The sample size was calculated using the THI minimal clinically important difference (MCID) of 7 points and a standard deviation (SD) of 14[17]. However, these values were reconsidered due to the consequent ineligibility of most tinnitus in-patients followed up by our otolaryngology service. From the wide range of THI MCID used in literature for this purpose[3,15], we arrived at a more conservative THI difference of 10 points with a SD of 13, corresponding to the CGI-I group "minimally better" of Zeman et al.[17] With 80.X% power, 0.05 α level, and a 10.X% dropout rate, the sample comprised 62 participants.

Randomization

Sequence generation . Participants were randomly assigned (1:1) to receive betahistine or a matching placebo. The sequence was generated by block randomization of six, and the allocation codified by aleatory numbers, using the software SAS (version 9.1).

Allocation concealment . Allocation concealment was performed using sequentially numbered, opaque and sealed envelopes, which were identified only by the randomization number.

Implementation . Eurofarma S.A. collaborators provided the allocation sequence, the active drug and placebo, and the allocation envelopes (eFigure 1 in Supplement). The principal investigator enrolled participants and the study clinical center (UPECLIN) pharmacy managed the intervention assignment and delivery.

Blinding

Investigators, participants, and statisticians were blinded to the treatment assignment, which was ensured by having active drug and matching placebo in identical boxes, pills, used in identical procedures, and with identical taste (eFigure 1 in Supplement). Eurofarma S.A. support team revealed the group identification only after the statistical analysis.

Statistical Methods

We conducted an intention-to-treat analysis for all randomized participants. Rubin's method of multiple imputations was used to estimate the treatment effect by combining five imputed values to complete missing data. Continuous parameters were compared using the Wilcoxon Mann-Whitney test; Hodges-Lehmann estimate was used to calculate a 95.0% confidence interval. Categorical variables were compared using the Fisher Exact test.

We also performed ancillary analysis by comparing THI subscales, using a multivariate regression model to adjust for the possible effect of 'education level' and 'guardian help to fill the THI score' on THI responsiveness, as well as 'mild hearing loss' and 'psychiatric illness' on clinical performance, and performed a sensitivity analysis to test the efficacy in those participants who completed the study, the per-protocol population.

We used Stata software (version 16.1) for all statistical analyses.

Results

Baseline Data

A volunteer sample of 284 individuals were screened, 186 were ineligible, and 36 declined to participate, (Figure 1; eTable 1 in Supplement). The remaining 62 participants were randomized into two groups of 31 participants each, one for betahistine and the other for the placebo. Of those enrolled, five were lost to follow-ups for reasons unrelated to the intervention, missing data at random. 57 participants completed the study, including the intervention and assessments. Out of those, 30 belonged to the placebo group and 27 to the betahistine group (Figure 1).

The median (IQR) age of the study population was 54 (48 to 60) years, with balanced sexes (male = 32; female = 30). The number (percentage) of participants that needed guardian help to fill the THI score was 14 (22.6%), with mild hearing loss was 45 (72.6%), occupation noise exposure was 6 (9.67%), migraine was 10 (16.13%), diabetes mellitus was 6 (9.7%) and with psychiatric illness was 12 (19.4%).

The median (IQR) tinnitus duration was 5 (2 to 10) years. The median (range) THI at baseline was 44 (30 to 60), and the THI subscales, functional, emotional, and catastrophic, were 16 (12 to 26), 16 (12 to 26), and 12 (8 to 14), respectively. Baseline demographic characteristics and THI are listed in Table 1, The location of tinnitus (right, left, or both ears), THI subscales, THI grade and the remaining baseline

demographic characteristics are listed in eTable 2 in Supplement. The betahistine group and the placebo group had balanced demographics and THI response (Table 1; eTable 3 in Supplement 1).

Primary Endpoint

Both study groups had effective adherence to treatment, the percentage of pills used was median (IQR) of 100.0% (98.0% to 100.0%) in the betahistine arm and a median (IQR) of 100.0% (96.0% to 100.0%) in the placebo arm. There was no difference in the THI change (THI before and after intervention) between the study groups (median difference of -2 points; 95.0% CI, -8 to 6 points) (U = 458.5, P =.75). The THI after the intervention was a median (IQR) of 4 (-4 to 14) points lower than before intervention in the betahistine arm and a median (IQR) of 2 (-6 to 10) points lower than before intervention in the placebo arm (Table 2; Figure 2).

Secondary Endpoint

The group's response was similar in all CGI-I seven-point scales and the participants' impression of the improvement question. Zero participants reported the highest level of change for better or worse (Table 2; Figure 3).

Ancillary Analyses

There was no difference in the THI subscales changes (functional, emotional, and catastrophic) between groups (Table 2).

The covariate adjustment multivariate and regression model revealed that the educational level, guardian help to fill the THI score, mild hearing loss, and psychiatric illness did not interfere in the efficacy results.

Also, the sensitivity analyses with per-protocol participants did not impact the study group baseline characteristics and the efficacy results (eTable 4 in Supplement 1).

Adverse Events

A total of 11 participants reported mild headache and gastrointestinal side effects, without groups differences; the number (percentage) in the placebo group was 3 (10), and of the betahistine group was 8 (29.63) (percentage difference, 19.63 (- 0.66 to 39.92; Table 2).

Discussion

Synopsis of key findings

This clinical trial demonstrated that betahistine is no more effective than a placebo to treat primary tinnitus. The THI score improvement was minimal and without significant difference between study groups. Additionally, the secondary endpoint, covariate adjustment, and per-protocol analysis provided similar results and side effects were without difference across both groups.

Comparison with other studies

In the recent systematic review by Wegner et al.,[3] the lack of rigorous clinical trials on Betahistine for primary tinnitus was evident, including only five studies. Also, it was not possible to prove the efficacy of this treatment (305 participants) as all studies had methodological flaws such as non-standardized outcome measures, heterogeneous dosages, unrepresentative samples, weak randomization, and unreliable blinding. Thus, the quality of evidence ranged from moderate to very low, making the results inconclusive.[3]

An alternative reference source of clinical trials using betahistine for tinnitus is studies pertaining to Ménière disease[6]. A recent systematic review failed to prove the efficacy of betahistine for Ménière symptoms such as tinnitus, also been represented by poor quality trials[6]. Although, unlike primary tinnitus studies, Adrion et al.[18] conducted a multicentric high-quality trial testing low dose (2 x 24 mg daily) and high dose (3 x 48 mg daily) betahistine against placebo, giving more confidence to betahistine inefficacy. However, the

extrapolation of these results for primary tinnitus is limited by possible differences in the pathophysiology of these conditions[3].

In contrast to previous trials, Ganança et al.[10]conducted a case-control study of patients with tinnitus and vestibular symptoms showing beneficial effects of betahistine in cases as opposed to controls who received no treatment (32.5% vs. 17.1%). Its large sample was an advantage over the Wegner et al.[3]systematic review (865 vs. 305), but the poor control of bias of observational design compromised a valid conclusion of betahistine efficacy.

Strengths and limitations of the study

The prevalent use and scarcity of reliable publications on this drug support the need for rigorous studies.[3] In response, we are presenting a trial that strictly followed SPIRIT guidelines and CONSORT statements. Therefore, we had certain strengths as an adequate sample, randomized, triple blinding, placebo-controlled design, participants retention, a standard betahistine posology and tinnitus endpoint. In addition, the broad recruitment of a general population increased the representativeness of our sample, improving the external validity of the study.

The small sample size limits the results' generalizability and made it impossible to explore the heterogeneity of performance between specific subgroups of the study population (such as those with migraine, psychiatric disorders, and hearing loss). Furthermore, the absence of anxiety and quality of life questionnaires reduced outcome inferences, and protocol changes (mainly sample size reduction) could have affected the accuracy of the study.

Clinical applicability

Betahistine is one of the most used empirical treatments, requiring a better scientific approach. To the best of our knowledge, this randomized clinical trial is the first reliable study to test this treatment for this purpose. Our results reveal that this drug is ineffective for primary tinnitus in adults, therefore, its large-scale use is likely to be of no benefit to patients. We believe that this result can avoid the negative impact of the use of ineffective treatments by these patients.

Conclusion

Betahistine was ineffective when compared to the placebo in the treatment of the primary tinnitus.

Figure Legend:

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Participant Flow Diagram

Numbers of study participants approached, enrolled and followed up for 3 months. Ineligibility may be due to more than 1 reason.

Figure 2. Box and Whisker Plot of Tinnitus Handicap Inventory (THI) Change

Distribution of THI change before and after intervention between both study groups (31 participants in each group). The ends of the boxes indicate the upper and lower quartile, the middle lines the median, and the whiskers the minimum and maximum values.

Figure 3. CGI-I Response Summary per Study Group

The distribution of Clinical Global Impression Improvement (CGI-I) response between both study groups (31 participants in each group). The bars indicate the number of participants per CGI-I scale.

Table 1. Demographics and THI Response of Study Participants[a]

Characteristic	**Placebo (n = 31)**	**Betahistine (n = 31)**	**Total (n = 62)**
Age, median (IQR), y	54 (48 to 60)	56 (47 to 64)	54 (48 to 60)

Characteristic	Placebo (n = 31)	Betahistine (n = 31)	Total (n = 62)
Sex, no. (%)			
Males	15 (48.39)	17 (54.84)	32 (51.61)
Females	16 (51.61)	14 (45.16)	30 (48.39)
Race, no. (%)			
White	27 (87.10)	30 (96.77)	57 (91.94)
Black	1 (3.23)	0 (0)	1 (1.61)
Others	3 (9.68)	1 (3.23)	4 (6.45)
Educational level, no. (%)			
Primary incomplete	4 (12.9)	6 (19.35)	10 (16.13)
Primary	0 (0)	2 (6.45)	2 (3.23)
Secondary incomplete	0 (0)	4 (12.9)	4 (6.45)
Secondary	14 (45.16)	13 (41.94)	27 (43.55)
Tertiary	13 (41.94)	6 (19.35)	19 (30.65)
Guardian help to fill the THI score, no. (%)	5 (16.13)	9 (29.03)	14 (22.58)
Mild Hearing loss, no. (%)	24 (77.42)	21 (67.74)	45 (72.58)
Occupational noise, no. (%)	3 (9.67)	3 (9.67)	6 (9.67)
Diabetes mellitus, no. (%)	3 (9.68)	3 (9.68)	6 (9.68)
Psychiatric illness, no. (%)	8 (25.81)	4 (12.9)	12 (19.35)
Migraine, no. (%)	5 (16.13)	5 (16.13)	10 (16.13)
Tinnitus duration, median (IQR), y	6 (3 to 10)	5 (2 to 8)	5 (2 to 10)
THI, median (IQR)	44 (30 to 68)	44 (28 to 62)	44 (30 to 66)

Abbreviations: THI – Tinnitus Handicap Inventory; y – year.[a] Data are presented as median\souts (IQR) for continuous data and in numbers (percentages) for categorical data.

Table 2. Comparison of Primary and Secondary Endpoints and Adverse Events Between Study Groups[a]

Measures	Placebo (n = 31)	Betahistine (n = 31)	Difference (95%CI) [b]
THI Change, median (IQR)	2 (-6 to 10)	4 (-4 to 14)	-2 (-8 to 6)
THI Subclass, median (IQR)			
Functional	6 (0 to 14)	6 (.58 to 11.44)	0 (-4 to 4)
Emotional	6 (0 to 10)	6 (-2 to 13.94)	0 (-4 to 4)
Catastrophic	0 (-8 to 14)	3.97 (-8 to 12)	0 (-8 to 8)
CGI-I, no. (%)			
Very Much Improved	0 (0)	0 (0)	0 (0)
Much Improved	0 (0)	3 (9.68)	9.68 (-0.7 to 20)
Minimally Improved	2 (6.45)	6 (19.35)	12.9 (- 3.4 to 29.28)
No Change	23 (74.19)	20 (64.52)	-9.68 (-32.5 to 13.15)

Measures	Placebo (n = 31)	Betahistine (n = 31)	Difference (95%CI) [b]
Minimally Worse	5 (16.13)	2 (6.45)	-9.6 8 (-5.9 to 25.25)
Much Worse	1 (3.23)	0 (0)	-3.22 (-9.4 to 2.93)
Very Much Worse	0 (0)	0 (0)	0 (0)
Impression of improvement, no. (%)			
Yes	1 (3.23)	5 (16.13)	12,9 (- 1.46 to 27.26)
Adverse Events, no. (%)	n = 30 (1 dropout)	n = 27 (4 dropout)	
Yes	3 (10)	8 (29.63)	19.63 (- 0.66 to 39.92)

Abbreviations: THI – Tinnitus Handicap Inventory; CGI-I – Clinical Global Impression Improvement.

[a] Data are presented as median\souts (IQR) for continuous data and in numbers (percentages) for categorical data.

[b] The 95% CI values represent risk differences for categorical variables and medians differences (Hodges-Lehmann estimate) for continuous variables.

References

1. McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity.*Hear Res.* 2016;337:70-9. doi:10.1016/j.heares.2016.05.009.
2. Tunkel DE, Bauer CA, Sun GH, et al. Clinical practice guideline: Tinnitus. *Otolaryngol - Head Neck Surg (United States).*2014;151(2):S1-S40. doi:10.1177/0194599814545325.
3. Wegner I, Hall DA, Smit AL, McFerran D, Stegeman I. Betahistine for tinnitus. *Cochrane Database Syst Rev.* 2018 Dec 28;12(12):CD013093. doi: 10.1002/14651858. .
4. Piccirillo JF, Rodebaugh TL, Lenze EJ. Tinnitus. *JAMA* . 2020;323(15):1497-98. doi:10.1001/JAMA.2020.0697.
5. McFerran DJ, Stockdale D, Holme R, Large CH, Baguley DM. Why is there no cure for tinnitus? *Front Neurosci* . 2019;13:1-13. doi:10.3389/fnins.2019.00802.
6. Van Esch B, van der Zaag-Loonen H, Bruintjes T, van Benthem PP. Betahistine in Ménière's Disease or Syndrome: A Systematic Review.*Audiol Neurotol.* Published online January, 2022;27(1):1-33. doi: 10.1159/000515821.
7. Mcferran D, Hoare DJ, Carr S, Ray J, Stockdale D. Tinnitus services in the United Kingdom: A survey of patient experiences. *BMC Health Serv Res.* 2018 Feb 13;18(1):110. doi: 10.1186/s12913-018-2914-3.
8. Dziadziola DJK, Laurikainen DEL, Rachel DJD, Quirk DWS. Betahistine Increases Vestibular Blood Flow. *Otolaryngol Head Neck Surg.*2016;120(3):400-5. doi:10.1016/S0194-5998(99)70283-4.
9. Unemoto H, Sasa M, Takaori S, Ito J, Matsuoka I. Inhibitory effect of betahistine on polysynaptic neurons in the lateral vestibular nucleus.*Arch Otorhinolaryngol.* 1982;236(3):229-36. doi:10.1007/BF00454214.
10. Ganança MM, Caovilla HH, Gazzola JM, Ganança CF, Ganança FF. Betahistine in the treatment of tinnitus in patients with vestibular disorders. *Braz J Otorhinolaryngol.* 2011;77(4):499-503. doi:10.1590/S1808-86942011000400014.
11. Sereda M.et al. A Process for Prioritising Systematic Reviews in Tinnitus. *Int J Audiol.* 2020; 59 (8): 640–6. doi:10.1080/14992027.2020.1733677.
12. Gupta A, Monsell EM. Which Patients With Asymmetric Sensorineural Hearing Loss Should Undergo Imaging? *Laryngoscope.*2018;128(9):1990-91. doi:10.1002/lary.27118.
13. Electronic Medicines Compendium. *Betahistine dihydrochloride.*https://www.medicines.org.uk/emc/product/7053/smp Published 2014. Accessed May 10, 2022.

14. Alves FPE, Cunha F, Onishi ET, Branco-Barreiro FCA, Ganança FF. Tinnitus handicap inventory: cross-cultural adaptation to Brazilian Portuguese. *Pro Fono.* 2005;17(3):303-10. doi:10.1590/S0104-56872005000300004.
15. Newman CW, Jacobson GP, Spitzer JB. Development of the tinnitus handicap inventory. *Arch Otolaryngol - Head Neck Surg.*1996;122(2):143-8. doi:10.1001/archotol.1996.01890140029007.
16. Busner J, Targum SD. The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry (Edgmont).*2007;4(7):28-37.

http://www.ncbi.nlm.nih.gov/pubmed/20526405. Accessed May 7, 2021.

Zeman F, Koller M, Figueiredo R, et al. Tinnitus handicap inventory for evaluating treatment effects: Which changes are clinically relevant? *Otolaryngol - Head Neck Surg.* 2011;145(2):282-7. doi:10.1177/0194599811403882.

Adrion C, Fischer CS, Wagner J, Gürkov R, Mansmann U, Strupp M; BEMED Study Group. Efficacy and safety of betahistine treatment in patients with Meniere's disease: Primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). *BMJ.* 2016;352:h6816. doi:10.1136/bmj.h6816.

Hosted file

`Figure 1.docx` available at https://authorea.com/users/495271/articles/577062-the-efficacy-of-betahistine-dihydrochloride-in-the-treatment-of-primary-tinnitus-a-randomized-clinical-trial-study

Figure 2. Box and Whisker Plot of the THI Change by Study Group

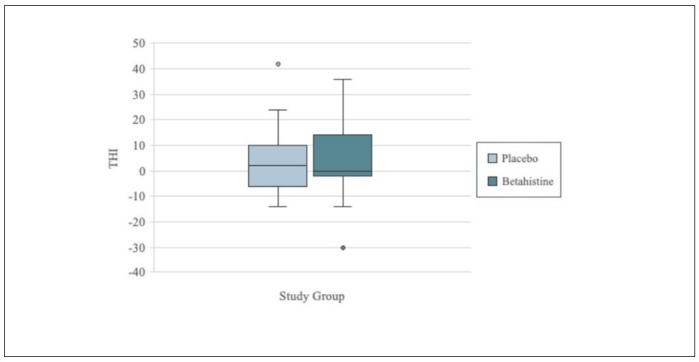

Figure 3. CGI-I Responses by Study Group