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Betahistine in Ménière's Disease or Syndrome: A Systematic Review

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Keywords
Ménière's disease · Therapy · Systematic review · Randomized controlled trials

Abstract

Background: Ménière's disease is characterized by recurrent episodes of vertigo, hearing loss, and tinnitus, often with a feeling of fullness in the ear. Although betahistine is thought to be specifically effective for Ménière's disease, no evidence for a benefit from the use of betahistine exists, despite its widespread use. Reassessment of the effect of betahistine for Ménière's disease is now warranted. ***Search Methods:*** We searched for randomized controlled trials (RCTs) in the Central Register of Controlled Trials (CENTRAL), Ovid Medline, Ovid Embase, CINAHL, Web of Science, Clinicaltrials.gov, ICTRP, and additional sources for published and unpublished trials, in which betahistine was compared to placebo. ***Data Collection and Analysis:*** Our outcomes involved vertigo, significant adverse effect (upper gastrointestinal discomfort), hearing loss, tinnitus, aural fullness, other adverse effects, and disease-specific health-related quality of life. We used GRADE to assess the quality of the evidence. ***Main Results:*** We included 10 studies: 5 studies used a crossover design and the remaining 5 were parallel-group RCTs. One study with a low risk of bias found no significant difference between the betahistine groups and placebo with respect to vertigo after a long-term follow-up period. No significant difference in the incidence of upper gastrointestinal discomfort was found in 2 studies (low-certainty evidence). No differences in hearing loss, tinnitus, or well-being and disease-specific health-related quality of life were found (low- to very low-certainty of evidence). Data on aural fullness could not be extracted. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated in the other adverse effect outcome with respect to dull headache. The pooled risk ratio for other adverse effect in the long term demonstrated a lower risk in favor of placebo over betahistine. ***Conclusions:*** High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, one study with low risk of bias found no evidence of a difference in the effect of betahistine on the primary outcome, vertigo, in patients with Ménière's disease when compared to placebo. The main focus of future research should be on the use of comparable outcome measures by means of patient-reported outcome measures.

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Introduction

Ménière's disease is characterized by recurrent episodes of vertigo, hearing loss, and tinnitus, often with a feeling of fullness in the ear. Vertigo attacks can occur without warning, and their intensity varies, which may lead to psychological suffering and a reduction in quality of life. The disorder may be subdivided into 2 categories: it may be secondary to a number of established inner ear disorders (Ménière's syndrome) or idiopathic (Ménière's disease). Ménière's disease is known to be associated with endolymphatic hydrops, that is, raised endolymph pressure in the membranous labyrinth of the inner ear [Hallpike and Cairns, 1938]. However, hydrops per se does not explain all its clinical features. Nonetheless, both categories may be considered as 1 entity, as in both, endolymphatic hydrops is the pathophysiological hallmark of the disease.

The diagnostic process may be difficult, as there is great variability in clinical presentation, and no reference standard exists. The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines [Alford, 1972], which have been revised twice [Pearson and Brackman, 1895; Committee on Hearing and Equilibrium, 1995]. The AAO-HNS 1995 guidelines formulate that a "definite" diagnosis can be made on the basis of at least 2 spontaneous episodes of rotational vertigo lasting at least 20 min, audiometric confirmation of sensorineural hearing loss, and tinnitus and/or a perception of aural fullness (see online suppl. Table 1; see www.karger.com/doi/10.1159/000515821 for all online suppl. material). More recently, diagnostic criteria have also been proposed by the Bárány Society [Lopez-Escamez et al., 2015].

In a recent study in the USA, the prevalence of Ménière's disease was estimated at 200 per 100,000 people per year [Alexander and Harris, 2010]. Ménière's disease is most common between 40 and 60 years of age [Harcourt et al., 2014]. Vertigo episodes tend to occur in clusters with a period of remission that may last for several months in between the clusters [Perez-Garrigues et al., 2008]. Episodes have been observed to occur with increasing frequency over the first few years after presentation and then decrease in association with a sustained deterioration in hearing [Moffat and Ballagh, 1997]. In most cases, vertiginous episodes eventually cease completely [Silverstein et al., 1989]. The fluctuating, progressive, and unpredictable natural history of Ménière's disease makes investigation of any treatment effect difficult; studies, therefore, need to compare interventions with placebo over an adequate time period. The aim of treatment is to reduce the number, severity, and duration of attacks of vertigo; to prevent progression of the disease and the loss of hearing; and to alleviate any chronic symptoms (e.g., tinnitus and aural fullness).

Betahistine dihydrochloride (betahistine) is an oral drug that has been prescribed to an estimated 130 million people worldwide since its first launch [Jeck-Thole and Wagner, 2006]. Although betahistine has been used for vestibular vertigo in general [Murdin et al., 2016], it is thought by some clinicians to be specifically effective for Ménière's disease [Martinez, 1972; Nauta, 2013]. The recommended daily dose of betahistine is 24–48 mg per day divided into 2 or 3 single doses containing 8, 16, or 24 mg [Jeck-Thole and Wagner, 2006]. Although gastrointestinal side effects are cited in many formularies, the rate of adverse effects in patients taking betahistine is not significantly different from those taking placebo in comparison studies [Murdin et al., 2016].

Betahistine is a weak histamine H1 receptor agonist and a potent histamine H3 receptor antagonist. The mechanism of action of the drug may be via the reduction of endolymphatic pressure through improved microvascular circulation in the stria vascularis of the cochlea [Meikle et al., 2012]. In addition, inhibition of activity in the vestibular nuclei may contribute to rebalancing neural activity and expedite the recovery process [Timmerman, 1994; Lacour et al., 2007]. Studies have shown that betahistine reaches a peak plasma concentration in about 1 h, and it has a plasma half-life of approximately 3.5 h. The maximal vestibular therapeutic effect will last approximately 3–4 h [Electronic Medicines Compendium, 2015]. The washout period can be calculated as 4 times the drug effect [Senn and Ezzez, 1999]. These pharmacological characteristics are thought to reduce the intensity and duration of vertigo symptoms in the short term (under 3 months) and additionally prevent attacks in the longer term (over 3 months).

A previous review found insufficient evidence of a benefit from the use of betahistine [James and Burton, 2001]. Despite this, it is still widely used and studied in clinical practice, especially in Europe. Reassessment of the effect of betahistine in the treatment of Ménière's disease is therefore now warranted.

Methods

Criteria for Considering Studies for This Review

Types of Studies

Randomized controlled trials (RCTs), including cluster RCTs, were included. We excluded quasi-randomized studies.

Crossover trials were eligible only if data before the crossover were extractable to avoid the potential for a carryover phenomenon.

Types of Participants

Patients with Ménière's disease or syndrome were included. We classified studies according to the diagnostic criteria used for Ménière's disease. We rated studies using the AAO-HNS or the Japanese Society of Equilibrium Research criteria to define probable, definite, or certain Ménière's disease as class "I" studies and studies using other diagnostic definitions as class "II." We rated studies including patients with "possible" Ménière's disease as class "III." Studies including participants who had received treatment with betahistine in the past were also eligible for inclusion.

Types of Interventions

Betahistine of any dose regimens or formulations and for any duration of treatment was included. The sole comparison was betahistine versus placebo. Concurrent use of other medication or other treatment was accepted if used equally in each group; for example, betahistine with an additional intervention versus placebo with an identical additional intervention. Where an additional intervention was used equally in both groups, we analyzed this as a separate comparison. None of the selected studies evaluated the effect of betahistine by concurrent use of other treatment.

Types of Outcome Measures

We analyzed the following outcomes in the review, but these were not used as a basis for including or excluding studies. Based on the pharmacological properties of the drug described above, we assessed outcomes as short term (3 months or under) or long term (3 months or over).

Primary Outcomes

The primary outcomes were the proportion of patients with a reduction in vertigo symptoms (considering the intensity, frequency, and duration of those symptoms altogether) and significant adverse effects including upper gastrointestinal discomfort.

Secondary Outcomes

The secondary outcomes were the proportion of patients with a progression of hearing loss (>15 dB), based on the 4-tone average of thresholds at 0.5, 1, 2, and 3 kHz, as measured by a pure-tone audiogram; the proportion of patients with a reduction in tinnitus, measured with patient-reported questionnaire scores such the Tinnitus Handicap Index (THI) ([Kleinstäuber et al., 2015]; see online suppl. Table 2), the Tinnitus Functional Index [Meikle et al., 2012], the Tinnitus Handicap Questionnaire [Kuk et al., 1990], the Tinnitus Questionnaire [Hallam, 1996], the Tinnitus Reaction Questionnaire [Wilson et al., 1991], and the Tinnitus Severity Scale [Sweetow and Levy, 1990]; the proportion of patients with a reduction in aural fullness, measured by patient-reported questionnaire scores (e.g., visual analog scale); other adverse effects (headache and allergic skin reactions [pruritus and rashes]); and well-being and disease-specific health-related quality of life: overall changes as reported particularly on the Functional Level Scale (FLS) (see online suppl. Table 3), the Ménière's Disease Patient-Oriented Symptom-Severity Index (MPOSI), and the Dizziness Handicap Inventory (see online suppl. Table 4). The FLS will be used as defined by the AAO-HNS 1995 guideline [Committee on Hearing and Equilibrium, 1995]. The questionnaires are validated and often used in trials to assess the changes in dizziness-related and Ménière's disease-related quality of life [Duracinsky et al., 2007]. We anticipated that various non-validated tools (e.g., questionnaires) were used. We included validated tools only to ensure that the outcomes were as reliable as possible.

Search Methods for Identification of Studies

The Cochrane Ear, Nose and Throat Disorders Group (CENTDG) Information Specialist conducted systematic searches for RCTs and controlled clinical trials. There were no language, publication year, or publication status restrictions. The date of the search was 29 January 2019.

Electronic Searches

Published, unpublished, and ongoing studies will be identified by searching the following databases from their inception: the Cochrane ENT Register (searched via Cochrane Register of Studies [CRS] to date); the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via CRS 16 January 2018, rerun on 29 January 2019); Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® (1946 to 16 January 2018, rerun on 29 January 2019); Ovid Embase (1974 to 16 January 2018, rerun on 29 January 2019); LILACS (searched on 16 January 2018 and rerun on 29 January 2019); Web of Knowledge and Web of Science (1945 to 16 January 2018 and rerun on 29 January 2019); ClinicalTrials.gov (www.clinicaltrials.gov,searched via the CRS 16 January 2018 and rerun on 29 January 2019); World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched on 16 January 2018 and rerun on 29 January 2019). The Information Specialist modeled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs and controlled clinical trials (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Box 6.4.b. [Handbook 2011]). Search strategies for major databases including CENTRAL are provided in online suppl. Table 5. This paper was written according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (see PRISMA checklist) [Moher et al., 2009].

Searching Other Resources

We scanned the reference lists of the identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials, and run non-systematic searches of Google Scholar to retrieve gray literature and other sources of potential trials.

Data Collection and Analysis

Selection of Studies

Two authors (B.E. and H.Z.-L.) independently selected studies to identify studies that appeared to meet the inclusion criteria. Both authors then reviewed the full-text articles of the retrieved trials and applied the inclusion criteria independently. We resolved any discrepancies by discussion or, failing that, by consultation of one of the other authors (T.B. and P.P.B.).

Data Extraction and Management

Two authors (B.E. and H.Z.-L.) independently extracted data from the studies using standardized data forms. We extracted data so as to allow an intention-to-treat analysis. If necessary or if insufficient data were provided in the paper, we contacted the authors for further information.

With regard to subgroup analysis, we extracted data to allow grading of the diagnostic accuracy of the methods used to define the study population (see Types of Participants), along with the duration of disease and treatment protocol (dose and duration of drug treatment). For the outcome "proportion of patients with a reduction in vertigo symptoms," we sought to independently dichotomize these into "improved" or "not improved." If we found studies with >2 groups (e.g., 2 or more active treatments compared to placebo), we extracted data from the intervention and placebo groups, but we made a note of the additional arm(s). If betahistine doses differed among the intervention groups within a study, we extracted data on the highest dose and compared this to placebo. Extraction of data on comorbidity involved, for example, the presence of migraine and benign paroxysmal positional vertigo. For each study, we extracted the following information: study design, duration of study, randomization, allocation concealment, number of participants, setting of study, diagnostic criteria, exclusion criteria, age and sex distribution of participants, country of recruitment, date of study, number of intervention groups, generic name of intervention, total dose per day (mg), method of administration, outcomes measured and definition of outcomes, missing data and final sample size, funding, conflict of interest (any author), and concomitant treatment.

Assessment of Risk of Bias in Included Studies

B.E. and H.Z.-L. assessed the risk of bias of the included studies independently, as guided by the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011). The "Risk of bias" tool addresses the following domains: sequence generation, allocation concealment, blinding, selective outcome reporting, incomplete outcome data, and other sources of bias (e.g., improper statistical analysis).

The 2 authors judged these domains using the Cochrane "Risk of bias" tool in RevMan 5.3 [RevMan, 2014], which involved describing each of these domains, as reported in the trial, and then assigning a judgment about the adequacy of each entry: "low," "high," or "unclear" risk of bias. We resolved differences of opinion by discussion. If no consensus was reached, one of the other authors was consulted.

Measures of Treatment Effect

The primary outcome in this review was the proportion of participants with a reduction in vertigo symptoms, which is a dichotomized measure. For this type of data, we aimed to calculate the risk ratio (RR). For intervention effect measures using continuous data, we planned to calculate the mean difference (MD) between groups, provided that the selected studies used the same scale of measurement and a validated tool. If different scales were used, we planned to calculate the standardized mean difference (SMD). For studies with ordinal data, we planned to dichotomize these data wherever possible.

Unit of Analysis Issues

Cluster Randomized Trials

We planned to include cluster RCTs with the cluster as the unit of analysis. However, none of the included studies were cluster RCTs.

Crossover Trials

In Ménière's disease, it is unlikely that symptom activity returns to its baseline level after the first treatment period. Therefore, we only used data from crossover trials only if the data prior to the crossover could be obtained.

Multi-Arm Studies

In the event that we found studies with >2 groups (e.g., 2 or more active treatments being tested against placebo), we established which of the comparisons were relevant to the systematic review. We found only 1 multi-arm study that used independent groups of participants. As a result, participants were not included in >1 group and were treated as independent comparisons.

Repeated Observations on Participants

The unit of analysis was the participant. We did not anticipate that by-ear reporting was available, but data per ear were preferred in cases of bilateral Ménière's disease. We regarded bilateral Ménière's disease patients as "improved" if any ear showed no deterioration of hearing loss and the proportion of patients who had a reduction in tinnitus or aural fullness increased. If studies evaluated the effect over a longer time period, we recorded the results at multiple time points. To avoid unit of analysis error when combining study results in a single meta-analysis (and therefore counting the same participants in >1 comparison), we defined different outcomes related to the periods of follow-up, and we performed separate analyses.

Dealing with Missing Data

Where necessary and where sufficient data from the study were not provided, we contacted the authors of the study requesting further details about missing data and reasons for the incompleteness of the data, in all those cases in which an email address was reported. We were alert to potential mislabeling or non-identification of standard errors and standard deviations. Our methods for imputation were according to chapter 7.7.3 of the Cochrane Handbook for Systematic Reviews of Interventions [Higgins and Green, 2011]. If data were missing, we used available case analysis using all data (as reported) for all randomized patients available at the end of the study/time point of interest, regardless of the actual treatment received. We considered the quality of outcome assessment as a study limitation (GRADE) and not as a stratifying factor. Unfortunately, we did not receive a useful response in any of the cases in which we contacted the authors. We did not impute missing data, as it remained unclear whether data were missing " at random" or " not at random."

Assessment of Heterogeneity

We determined whether the selected studies suffered from clinical, statistical, or methodological heterogeneity. We planned to quantify statistical heterogeneity using the I^2 statistic and the χ^2 test. With respect to the I^2 statistic, an approximate guide to interpretation is provided in the Cochrane Handbook for Systematic Reviews of Interventions [Higgins and Green, 2011]. If the I^2 value

was 50% or higher, we considered the data to suffer from substantial or considerable heterogeneity. For the χ^2 test, we used the indicator that if the χ^2 was greater than the degrees of freedom, then heterogeneity was likely to be present. We considered heterogeneity to be statistically significant if the p value was <0.10. Subsequently, we performed the meta-analysis using fixed-effect (in the absence of heterogeneity) and random-effects modeling (in the presence of heterogeneity).

Assessment of Reporting Biases

If an outcome was reported by at least 10 studies, we planned to assess publication bias using a funnel plot and Egger's test. Unfortunately, none of the outcomes were reported in this number of studies.

Data Synthesis

We planned to analyze treatment differences as an RR, calculated using the Mantel-Haenszel method. Unfortunately, none of the selected studies analyzed the outcomes by means of comparable or validated tools.

Subgroup Analysis and Investigation of Heterogeneity

There were insufficient data available for subgroup analyses. Although we planned to perform the following subgroup analyses, we were not able to do so for: stage of disease, as defined by the AAO-HNS 1995 guidelines (see online suppl. Table 6); type of Ménière's disease (see Types of Participants); and dose of betahistine administered (minimum daily dose of 8 mg to a maximum of 148 mg).

Sensitivity Analysis

We planned to conduct a sensitivity analysis by excluding those studies with a high risk of bias, thereby checking the robustness of the conclusion from the studies included in the meta-analysis. In addition, we planned to use sensitivity analyses for studies in which data were imputed. However, all but one study carried an unclear or high risk of bias, and in none of the studies, data were imputed.

GRADE and "Summary of Findings" Table

Two authors (B.E. and H.Z.-L.) independently used the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct, and we applied this in the interpretation of results. There are 4 possible ratings of quality: high, moderate, low, and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that we are very uncertain about any estimate of effect obtained.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low, or very low. The degree of downgrading is determined by the seriousness of these factors: study limitations (risk of bias), inconsistency, indirectness of evidence, imprecision, and publication bias. We included a "Summary of findings" table for our comparison of betahistine versus placebo, constructed according to the recommendations described in chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions [Higgins and Green, 2011], for the following outcomes: the primary outcomes vertigo (the proportion of patients with a reduction in vertigo symptoms) and significant adverse events (upper gastrointestinal discomfort) and the secondary outcomes hearing loss, tinnitus, aural fullness, other adverse effects (headache and allergic skin reaction), and well-being and disease-specific health-related quality of life.

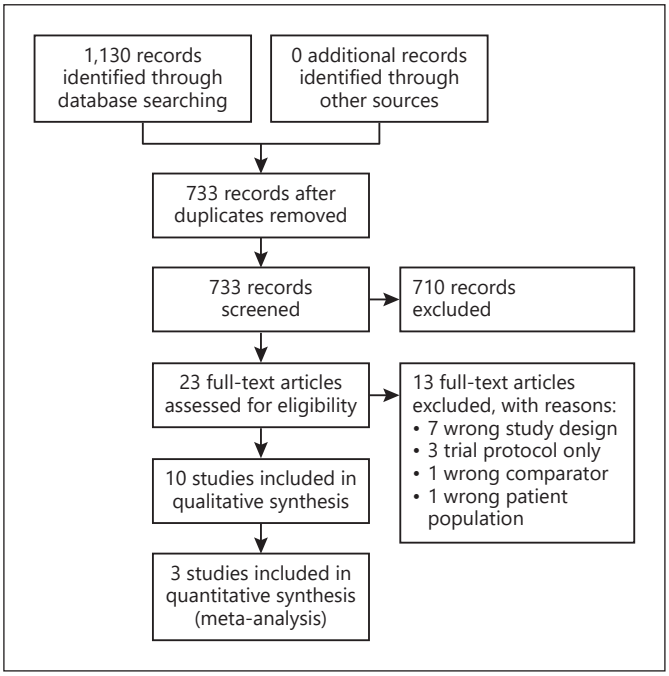


Fig. 1. Flowchart process for sifting search results and selecting studies for inclusion.

Results

Results of the Search

The electronic database search was performed by the Cochrane ENT Information Specialist on 29 January 2019 and identified 1,130 records in total. No additional records were identified through other sources. This number dropped to 733 after the removal of duplicates. We screened the 733 records and found 710 to be irrelevant. We were left with 23 potentially eligible studies. We excluded 13 of these studies with reasons (see Excluded Studies). We identified 10 studies meeting the inclusion criteria in terms of study design, participants, and interventions. No further eligible records were identified from a handsearch of the reference lists. There are no studies awaiting assessment, and we identified no ongoing studies. The study selection process is shown in Figure 1.

Table 1. Adrion [2016]

Methods	**Study design:** RCT **Study grouping:** parallel group
Participants	**Sample size** Number randomized: 221 participants were allocated to high-dose betahistine, low-dose betahistine, or placebo for a 9-month follow-up; 74 were allocated to the placebo group, 73 to the low-dose betahistine group, and 74 to the high-dose betahistine group. Number completed: 72 in the placebo group, 70 in the low-dose betahistine group, and 72 in the high dose betahistine group **Participants baseline characteristics** Age: mean age for placebo, 54.5 (SD 12.8); low-dose betahistine, 56.1 (SD 11.1); and high-dose betahistine, 56.1 (SD 12.6). Gender: male (%) – for placebo, 35 (47); low-dose betahistine, 39 (53); high-dose betahistine, 35 (47); and total 109 (49) **Inclusion criteria**: patients aged 18–80 years were eligible for enrolment if they presented with 2 or more definitive spontaneous episodes of vertigo of at least 20 min' duration, had audiometrically documented hearing loss on at least 1 occasion, and tinnitus or aural fullness in the treated ear, excluding other possible causes of vertigo. These factors made up a diagnosis of definite unilateral or bilateral Ménière's disease, fulfilling the criteria of the 1995 AAO-HNS guideline. Furthermore, patients had to be in an active phase of the disease, with at least 2 vertigo attacks per month in at least 3 consecutive months before enrolment. Female patients of childbearing potential were only included if they had a negative serum pregnancy test within 7 days before initiation of treatment and were willing to practice acceptable methods of birth control during treatment and for 3 months after treatment; class I **Exclusion criteria**: exclusion criteria were diagnosis of other central or peripheral vestibular disorders such as vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, and phobic postural vertigo. Patients were excluded if they had known contraindications or sensitivity to betahistine, such as bronchial asthma, pheochromocytoma; treatment with other antihistamine drugs; ulcer of the stomach or duodenum; or severe dysfunction of the liver or kidney. Safety-related exclusion criteria were severe coronary heart disease or heart failure, persistent uncontrolled hypertension with systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg, life expectancy <12 months, other serious illness, or a complex disease that might confound treatment assessment. General exclusion criteria were participation in another trial with an investigational drug or device within the past 30 days, previous participation in the present study, or planned participation in another trial **Pretreatment:** not reported
Intervention	**Intervention group** Low-dose betahistine: 24 mg per capsule, 6 capsules 3 times per day, leaving with 4 capsules with placebo and 2 capsules in the morning and evening with betahistine, betahistine dihydrochloride tablets were over-encapsulated with mannitol and Aerosil as filling material High-dose betahistine: 3 times daily 48 mg, 2 capsules 3 times daily, betahistine dihydrochloride tablets were over-encapsulated with mannitol and Aerosil as filling material **Comparator group:** placebo was an identically appearing capsules filled with mannitol and Aerosil but not containing any active ingredient, which was administered 3 times daily **Use of additional interventions:** none reported, change in relevant concomitant drug treatment was registered
Outcomes	The effect on vertigo was calculated by means of the log-transformed number per 30 days interval, in which only changes from baseline were shown comparing the high- and low-dose betahistine to placebo The incidence of adverse effects was evaluated at 9 months The effect on hearing loss was calculated by adjusted mean changes by means of comparing with the placebo group for the high- and low-dose betahistine group; results were only presented per frequency The effect on tinnitus was based on the MiniTF questionnaire. Only the adjusted mean change for the placebo was given, whereas, similar to all other outcomes, the results for high-dose and lose-dose betahistine were based on the difference in comparison to placebo The effect on aural fullness was not reported although shown at baseline characteristics table The incidence of adverse effect was evaluated at 9 months The effect on disease-specific health-related quality of life was analyzed, similar to tinnitus with the adjusted mean change comparing placebo to low and high dose of betahistine

Table 1 (continued)

Identification	Sponsorship source: funding: this study was not industry sponsored. The study was supported by grants from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung [BMBF], support code 01KG0708; sponsor's protocol code no. 04T-617). This work was supported by the German Centre for Vertigo and Balance Disorders (DSGZ), University Hospital Munich, Campus Grosshadern, Munich, Germany. The sponsor had no role in the design, management, data collection, analyses, or interpretation of the data or in the writing of the manuscript or the decision to submit for publication Country: Germany Setting: tertiary referral centers (14) Comments: none Author name: Christine Adrion Institution: German Center for Vertigo and Balance Disorders Email: Michael. strupp@med.uni-muenchen.de Address: University Hospital Munich, Campus Grosshadern, Munich, Germany	
Declaration of interest	Declared no conflict of interest	
Notes		
Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Low risk	Randomly assigned in a 1:1:1 ratio
Allocation concealment (selection bias)	Low risk	Concealment allocation was performed by an Internet-based randomization schedule stratified by study site; fixed block size was 3, which was not disclosed during the trial; random list was generated by an investigator with no clinical involvement in the trial
Blinding of participants and personnel (performance bias)	Low risk	Patients, clinicians, core laboratories, and trial staff were blinded to treatment allocation
Blinding of outcome assessment (detection bias)	Low risk	Patients, clinicians, core laboratories, and trial staff were blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Reasons for dropouts were given for all participants
Selective reporting (reporting bias)	Low risk	All predefined outcomes were analyzed
Other bias	Unclear risk	Pre-randomization attack frequency was not documented although considered as an inclusion criterion. Data were not shown with respect to duration and age at the onset of disease but groups were well balanced based on these characteristics

RCT, randomized controlled trial; AAO-HNS, American Academy of Otolaryngology Head and Neck Surgery.

Included Studies

We included 10 RCTs, the details of which are shown in the characteristics of included studies table (Tables 1–10). One of the included studies included >2 treatment arms [Adrion et al., 2016]. The study of Adrion et al. [2016] was a 3-arm study, which compared high-dose betahistine, low-dose betahistine, and placebo. This was also the only study to highlight no financial conflict of interest. We identified no unpublished industry studies.

Table 2. Burkin [1967]

Methods	**Study design:** RCT **Study grouping:** crossover	
Participants	**Sample size** Number randomized: 22 participants were allocated to either betahistine or placebo for 2 weeks and then switched to placebo or betahistine, 4-week follow-up period Number completed: 22 participants, unclear if this was equally balanced across both groups **Participants baseline characteristics** Age: not reported, calculated from raw data 47.1 (SD 5.1) Gender: 50% male **Inclusion criteria:** diagnosed as having Ménière's syndrome, careful examination of each patient and a thorough evaluation of their symptoms; class III **Exclusion criteria:** none predefined **Pretreatment:** unknown	
Interventions	Intervention group: betahistine tablets, 16 mg daily (4 mg 4 times a day) during 2 weeks Comparator group: placebo tablets, 4 times a day, during 2 weeks Use of additional interventions: none	
Outcomes	Dizziness – present or absent dichotomy Adverse events	
Identification	Sponsorship source: unknown Country: USA Setting: Department of Otolaryngology Comments: no comment Author name: Aaron Burkin Institution: Springfield Mercy and Wesson Memorial Hospitals Email: unavailable Address: unavailable	
Declaration of interest	Not given	
Notes		
Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was checked with several statistical tests," unclear which statistical tests were used and additional details on methods of randomization were not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear how blinding of participants and personnel was achieved. Quote: "the study was completely double-blind and neither the investigator nor the patient knew which tablet was the active and which the placebo."
Blinding of outcome assessment (detection bias)	Unclear risk	No details were given
Incomplete outcome data (attrition bias)	Unclear risk	No details were given
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcomes listed in the material and methods section of the article were all reported in the results section of the article
Other bias	Unclear risk	No details on statistical analyses were given on how group differences after therapy were calculated and whether these results were statistically significant

RCT, randomized controlled trial.

Table 3. Elia [1966]

Methods	**Study design:** RCT **Study grouping:** crossover
Participants	**Sample size** Number randomized: 20 participants were allocated to either betahistine (A or C) or placebo (B or D) for 2 weeks and then switched to placebo or betahistine. This was repeated for 2 more times Number completed: 16 participants, unclear whether this was equally balanced across both groups **Participants baseline characteristics** Age: not reported Gender: not reported **Inclusion criteria:** suffering from intractable vertigo for at least 4 months. Readily available for examination. Would agree to continue therapy for 8 weeks. Examination every 14 days; class III **Exclusion criteria:** none predefined **Pretreatment:** unknown
Interventions	**Intervention group:** betahistine tablets, 16 mg daily (4 mg 4 times a day) during 8 weeks **Comparator group:** placebo tablets, 4 times a day, during 8 weeks **Use of additional interventions:** all medication was discontinued 14 days prior to the patient being included in the study; no medication other than betahistine hydrochloride or placebo was taken by the patient during the period of this study; no information on protocol adherence was reported
Outcomes	Subjective change in vertigo based on a 4-point scale (0–3) Subjective change in tinnitus based on a 4-point scale (0–3) Subjective change in aural fullness based on a 4-point scale (0–3)
Identification	Sponsorship source: unknown Country: USA Setting: Washoe Medical Center and St. Mary's Hospital Comments: no comment Author name: Joseph C. Elia Institution: Washoe Medical Center and St. Mary's Hospital Email: unavailable Address: 275 Hill St. Reno, Nevada 89504
Declaration of interest	None declared
Notes	

Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Unclear risk	No details on whether the physician was unaware of the sequence generation
Allocation concealment (selection bias)	Low risk	Uninvolved fifth person generating sequence
Blinding of participants and personnel (performance bias)	High risk	The same sequence was repeated (A–D) and used in all patients and could be predicted by the patients, physician, and the statistician
Blinding of outcome assessment (detection bias)	High risk	The same sequence was repeated (A–D) and used in all patients and could be predicted by the patients, physician, and the statistician
Incomplete outcome data (attrition bias)	High risk	4 out of 20 participants dropped out due to noncompliance to the trial and change of location of the participants
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcomes listed in the material and methods section of the article are all reported in the results section of the article
Other bias	High risk	No details on how statistical analyses were performed although the authors concluded a positive effect was found for betahistine on Ménière's disease

RCT, randomized controlled trial.

Table 4. Frew [1976]

Methods	Study design: RCT Study grouping: crossover
Participants	**Sample size** Number randomized: 26 participants were allocated to either betahistine or placebo for 8 weeks and then switched to placebo or betahistine. This was repeated for 2 more times, with a total of 36 weeks Number completed: 22 participants, unclear whether this was equally balanced across both groups **Participants baseline characteristics** Age: not reported Gender: not reported **Inclusion criteria:** diagnosis was based on paroxysmal attacks of rotational vertigo, tinnitus, and fluctuating sensorineural deafness; class III **Exclusion criteria:** none predefined **Pretreatment:** unknown
Interventions	Intervention group: betahistine tablets, 16 mg daily (8 mg 2 times a day) during 36 weeks Comparator group: placebo tablets, 4 times a day, during 36 weeks Use of additional interventions: participants were prescribed placebo 4 weeks prior to the start of the trial
Outcomes	Subjective change in vertigo based on a 4-point scale (0–3) Subjective change in tinnitus based on a 4-point scale (0–3) Subjective change in aural fullness based on a 4-point scale (0–3)
Identification	Sponsorship source: Unknown Country: Holland Setting: Department of Otorhinolaryngology, Newcastle University Hospitals Group Comments: Philips Duphar's statistician was acknowledged Authors name: I.J.C. Frew Institution: Department of Otorhinolaryngology, Newcastle University Hospitals Group Email: unknown Address: Department of Otorhinolaryngology, Newcastle University Hospitals Group, no further details on the address were given
Declaration of interest	None declared
Notes	

Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Unclear risk	No details were given
Allocation concealment (selection bias)	Unclear risk	No details were given
Blinding of participants and personnel (performance bias)	Unclear risk	Physician could break the code if relapse occurred. Unclear if and in how many cases this occurred, blinding cannot be assured
Blinding of outcome assessment (detection bias)	Unclear risk	No details on blinding of outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	Unclear why 6 patients withdrew, described as "unable to cooperate," no reasons for dropout were described
Selective reporting (reporting bias)	High risk	Not all predefined outcomes were reported after assessment by the investigator. Unclear why not all outcomes were summarized by the investigator
Other bias	High risk	One-sided testing, which should be 2-sided; standard deviation not reported; high risk of selection bias due to pretreatment period, allowing the investigator to exclude placebo responders (decreases external validity of study results)

RCT, randomized controlled trial.

Table 5. Meyer [1985]

Methods	**Study design:** RCT **Study grouping:** crossover
Participants	**Sample size** Number randomized: 40 participants were allocated to either betahistine or placebo for 6 weeks and then switched to placebo or betahistine Number completed: 40 participants **Participants baseline characteristics** Age: 24–67 years Gender: 21 (56) **Inclusion criteria:** based on patient history, audiometric hearing test results, vestibular testing, radiologic results, neurological, and orthopedic research; class III **Exclusion criteria:** allergic reactions, gastritis, gastric ulcer, hypertonic, liver dysfunction (contraindication for use of betahistine) **Pretreatment:** 1 year before study treatment, during treatment (at 2, 6, and 12 weeks), and after 1 year, outcomes were measured
Interventions	Intervention group**:** betahistine dihydrochloride, participants were treated with 36 mg daily, 3 times daily 2 tablets Comparator group: placebo tablets, 3 times daily 2 tablets Use of additional interventions: none reported
Outcomes	Subjective change in vertigo based on a 4-point scale (0–3) Subjective change in tinnitus based on a 4-point scale (0–3) Subjective change in aural fullness based on a 4-point scale (0–3) Change in hearing loss was based on the mean 3-tone average of thresholds at 0.5, 1, and 2 kHz
Identification	Sponsorship source: unknown Country: Germany Setting: HNO-Klinik und Poliklinik Bereich Medizin der Humboldt-Universiat at Berlin Comments: no comment Author name: E.D. Meyer Institution: HNO-Klinik und Poliklinik Bereich Medizin der Humboldt-Universiat Berlin Email: unknown Address: Schumannstrasse 20/21, DDR–1040 Berlin
Declaration of interest	None declared
Notes	

Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Unclear risk	No details on sequence generation were given
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear which methods were undertaken to maintain blinding of participants and personnel
Blinding of outcome assessment (detection bias)	Unclear risk	No details on the method of blinding of the outcome assessors were given
Incomplete outcome data (attrition bias)	High risk	Impaired walking pattern for only 38 patients were reported, which implicates missing data, although no details on this matter were reported
Selective reporting (reporting bias)	High risk	Not all outcomes were predefined and details on how these were assessed (tinnitus, gate disturbances, and aural fullness)
Other bias	Unclear risk	Inclusion of patients was based on several additional diagnostic tests, although it remains unclear which diagnostic criteria were mandatory to fulfill the diagnosis of Ménière's disease, unclear which statistical analysis was used for each outcome

RCT, randomized controlled trial.

Table 6. Mira [2003]

Methods	**Study design:** RCT **Study grouping:** parallel group	
Participants	**Sample size** Number randomized: 41 participants were allocated to betahistine, and 40 participants were allocated to placebo for 3 months Number completed: 81 participants **Participants baseline characteristics** Age: not reported Gender: not reported **Inclusion criteria:** probable or possible MD based on the AAO HNS criteria, out- or inpatient, between 18 and 65 years of age, signed and informed written consent. Withdrawal of interfering concomitant therapies at least 7 days before start of the trial. Normal laboratory documented renal and hepatic functional cooperating by adhering to the scheduled procedure; class II **Exclusion criteria:** concomitant infectious and definite cerebrovascular diseases. Diseases that were not compatible with and were contraindicated by the treatment under study. Concomitant therapy with anti-vertigo drugs. Taking drugs that act on cerebral circulation (antihistamines, antiaggregant, thiazide diuretics, corticosteroids, and benzodiazepines), major or surgical condition likely to interfere with the absorption distribution, metabolics, or excretion of the drug used in the study, having a terminal disease **Pretreatment:** not reported	
Interventions	Intervention group: betahistine dihydrochloride, participants were treated with 32 mg daily, 16 mg 2 times per day Comparator group: placebo tablets, 2 times daily 2 tablets Use of additional interventions: none reported	
Outcomes	The effect on vertigo was reported by means of the mean number of vertigo attacks per month The incidence of significant adverse effects at 3 months Subjective change in tinnitus based on a 5-point scale (0–4) Subjective change in aural fullness based on a 5-point scale (0–4), and data were not specified for aural fullness The incidence of other adverse effects at 3 months The disease-specific health-related quality of life, based on a 3-point scale	
Identification	Sponsorship source: grant form Grunenthal-Formenti, Milan, Italy Country: Italy Setting: multicenter Comments: no comment Author name: Eugenio Mira Institution: University of Pavia Email: e.mira@smatteo.pv.it Address: not given	
Declaration of interest	None declared	
Notes		
Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Unclear risk	Unclear who made and kept the randomization list
Allocation concealment (selection bias)	Unclear risk	No details on the allocation concealment were given
Blinding of participants and personnel (performance bias)	Low risk	Attempts made to assure blinding

Table 6 (continued)

Blinding of outcome assessment (detection bias)	Low risk	Attempts made to assure blinding
Incomplete outcome data (attrition bias)	High risk	Not balanced across groups and related to outcome
Selective reporting (reporting bias)	Low risk	Results of all outcomes described
Other bias	High risk	No references on the determination of the sample size calculation were available; improvement of associated symptoms including tinnitus, fullness of the ear, nausea, and vomiting are summarized in 1 figure, whereas it remains unknown how calculations were performed, and unknown if complete data were available

RCT, randomized controlled trial; AAO-HNS, American Academy of Otolaryngology Head and Neck Surgery.

Design

In 5 out of 10 studies, a prospective, crossover comparison design was used [Burkin, 1967; Frew and Menon, 1976; Meyer, 1985; Schmidt and Huizing, 1992; Mira et al., 2003]. In 2 of these 5 studies, data prior to crossover were extractable. In the remaining 5 studies, a parallel group design was used. All studies were described as being double-blinded.

Sample Sizes

The sample size ranged from 10 [Ricci et al., 1987] to 221 [Adrion et al., 2016]. A total of 402 patients had results reported across the 10 included studies. No additional results from unpublished studies were included in this review.

Setting

All studies were conducted in otorhinolaryngology departments within hospitals. The majority of the studies were single-centered. The studies of Mira et al. [2003] and Adrion et al. [2016] were multicenter studies. The selected studies took place in Germany [Meyer, 1985; Adrion et al., 2016], the UK [Burkin, 1967; Frew and Menon, 1976], the USA [Elia, 1966], Italy [Salami et al., 1984; Ricci et al., 1987; Mira et al., 2003], Japan [Okamoto et al., 1968], and the Netherlands [Schmidt and Huizing, 1992].

Participants

All of the included studies described the recruited patients as having Ménière's disease, but different inclusion criteria and definitions for the disease were used. In the study of Adrion et al. [2016], the internationally recognized criteria for "definite" Ménière's disease were applied and it was therefore classified as class "I" (see Types of Participants). Both the studies of Schmidt et al. [1992] and Mira et al. [2003] used other diagnostic definitions, including patients with probable/possible Ménière's disease according to the AAO-HNS criteria and the Utrecht working definition, and we therefore classified them as class "II." We classified the studies of Elia [1966], Burkin [1967], Okamoto et al. [1968], Frew and Menon [1976], Salami et al. [1984], Meyer [1985], and Ricci et al. [1987] as class "III" since no specific predefined diagnostic criteria were provided or details on how vertigo attacks, hearing loss, and tinnitus were evaluated.

Interventions and Comparisons

All included studies evaluated the effect of betahistine. The daily betahistine dose that was used in the included studies varied: 16 mg [Elia, 1966; Burkin, 1967], 24 mg [Salami et al., 1984], 2 mg [Frew and Menon, 1976; Mira et al., 2003], 36 mg [Okamoto et al., 1968; Meyer 1985] (2 times daily with 3 pills), 72 mg [Schmidt and Huizing, 1992], and 144 mg [Ricci et al., 1987]. One study compared high-dose betahistine (144 mg per day, in 3 doses) and low-dose betahistine (48 mg per day, in 2 doses) to placebo [Adrion et al., 2016]. Schmidt and Huizing [1992] used a slow-release formulation. Assessment with regard to compliance was only reported in detail by Adrion et al. [2016]. None of the selected studies evaluated the effect of betahistine with concurrent use of other treatment. All studies used a placebo as the comparator.

Outcomes

Most of the selected studies only evaluated short-term effects (<3 months), except for Schmidt et al. [1992], Mira et al. [2003], and Adrion et al. [2016]. Adrion et al. [2016] evaluated the effects of all 3 interventions arms after 9

Table 7. Okamoto [1968]

Methods	**Study design:** RCT **Study grouping:** parallel group
Participants	**Sample size** Number randomized: 40 participants were allocated to betahistine or placebo Number completed: 36 participants, 2 dropouts in the betahistine and 2 dropouts in the placebo group **Participants baseline characteristics** Age: not reported Gender: 13 males (36%) **Inclusion criteria:** diagnosed as Ménière's disease from their anamnesis (past history) and through hearing examination and vestibular function examination. Patients had to suffer from accompanying paroxysmal vertigo, deafness, and tinnitus; class III **Exclusion criteria:** not defined **Pretreatment:** not reported
Interventions	Intervention group: betahistine dihydrochloride, 36 mg per day, 6 tablets per day, 2 times 3 tablets daily for 2 weeks Comparator group: 6 tablets per day, 2 times 3 tablets daily prepared identically in appearance, taste, and smell for 2 weeks Use of additional interventions: none reported
Outcomes	Subjective change in vertigo based on a 3-point scale (0–2) Subjective change in tinnitus based on a 3-point scale (0–2) Subjective change in hearing loss based on a 3-point scale (0–2) Change in the incidence of other adverse effects based on a 3-point scale (0–2)
Identification	Sponsorship source: Eisai Co., Ltd. Country: Tokyo Setting: The 2nd Tokyo National Hospital Comments: Author name: Ken Okamoto Institution: The 2nd Tokyo National Hospital Email: y-hayakawa@hhc.eisai.co.jp Address: unknown
Declaration of interest	None declared
Notes	Medication supplied by Eisai Co.; unclear what the role of the subsidizing party was

Risk of bias		
bias	author's judgment	support for judgment
Random sequence generations (selection bias)	Low risk	Drug bottles were labelled with a random serial number on a layout
Allocation concealment (selection bias)	Low risk	The table of random numbers was created by an independent third party from the medical institution
Blinding of participants and personnel (performance bias)	Low risk	In the discussion, it was claimed that both patients and doctors were unaware of the drug they had been given
Blinding of outcome assessment (detection bias)	Unclear risk	No methods on the blinding of outcome assessors were provided
Incomplete outcome data (attrition bias)	High risk	4 dropouts not due to adverse effect of the drug, unknown
Selective reporting (reporting bias)	Low risk	There was no protocol available, the outcomes listed in the method section of the article were all reported in the results section
Other bias	High risk	Medication supplied by Eisai Co.; unclear what the role of the subsidizing party was

RCT, randomized controlled trial.

Table 8. Ricci [1987]

Methods	**Study design:** RCT **Study grouping:** parallel group
Participants	**Sample size** Number randomized: 10 participants were allocated to betahistine or placebo, evaluated after 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment Number completed: 10 participants **Participants baseline characteristics** Age: betahistine 36.4 years (SD 2.2); placebo 37.0 years (SD 5.4) Gender: 6 males (60%) **Inclusion criteria:** Ménière's disease patients; class III **Exclusion criteria:** hypersensitivity against betahistine, peptic ulcer, gastroduodenitis, pheochromocytoma, asthma, grave asthenia, arterial hypertension, renal, or hepatic insufficiency Pretreatment: not reported
Interventions	Intervention group: betahistine hydrochloride 24 mg per day, 3 times a day at a meal, 16 drops, equal to 8 mg of active ingredient, for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment Comparator group: not reported Use of additional interventions: during the study, concomitant use of anti-vertigo drugs, drugs acting on the cerebral circulation, antihistamines, and histamines mimetics was prohibited
Outcomes	Subjective change in vertigo based on a 3-point scale (1–3) Change in objective hearing loss classified based on the mean hearing thresholds of 0.5, 1, and 2 kHz classified according to ANSI (6 classes) Subjective change in tinnitus based on a 7-point scale (0–6) Subjective change in aural fullness based on a 7-point scale (0–6)
Identification	Sponsorship source: not reported Country: Italy Setting: University of Verona Comments: Author name: V. Ricci Institution: Universita degli Studi di Verona Email: not available Address: Clinica Otorinolaringoiastica; Universita di Verona, 37100 Verona
Declaration of interest	None declared
Notes	

Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Low risk	Assigned to the treatment groups based on a randomization list
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was available
Blinding of outcome assessment (detection bias)	Unclear risk	No information was available on blinding of the outcome assessors
Incomplete outcome data (attrition bias)	Unclear risk	No dropouts or lost to follow-up were reported
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcomes listed in the material and methods section of the article are all reported in the results section of the article
Other bias	Unclear risk	No information was available regarding the performed statistical analyses

RCT, randomized controlled trial.

Table 9. Salami [1984]

Methods	**Study design:** RCT **Study grouping:** parallel group	
Participants	**Sample size** Number randomized: 15 participants were allocated to betahistine and 15 participants were allocated to the placebo who were evaluated after 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment during 6 weeks Number completed: 30 participants **Participants baseline characteristics** Age: betahistine 49.6 years (SD 4); placebo 42.7 years (SD 3.5) Gender: 17 males (56%) **Inclusion criteria:** Vascular or neurovascular Ménière's syndrome, criteria for diagnosis were not stated; class III **Exclusion criteria:** patients with vertigo of extra-vestibular origin (visual and proprioceptive mental); patients with a history of peptic ulcer, pheochromocytoma, asthma, ictus cerebri (cerebral shock, exhaustion [grave asthenia]), and arterial hypertension; patients with hepatic or renal insufficiency; patients with alteration in gonad or thyroid function; those exposed to prolonged treatments with drugs that are potentially ototoxic (quinine, salicylates, aminoglycoside, and furosemide); those regularly using narcotics; lactating or pregnant women; and those with a proven hypersensitivity to betahistine hydrochloride Pretreatment: not reported	
Interventions	Intervention group: betahistine hydrochloride 24 mg per day, 3 times a day at a meal, 16 drops, equal to 8 mg of active ingredient, for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment Comparator group: not reported Use of additional interventions: during the study, concomitant use of anti-vertigo drugs, drugs acting on the cerebral circulation, antihistamines, and histamines mimetics was prohibited	
Outcomes	Subjective change in vertigo based on a 4-point scale (0–3) Objective change in hearing loss classified based on the mean hearing thresholds of 0.5, 1, 2, and 3 kHz Subjective change in tinnitus based on a 7-point scale (0–6) Subjective change in aural fullness based on a 7-point scale (0–6)	
Identification	Sponsorship source: not applicable Country: Italy Setting: otorhinolaryngology outpatient department Comments: Author name: A. Salami Institution: Clinica Otorinolaringoiatrica B dell'Univerisita Email: not available Address: Viale Benedetto XV, 16132 Genova	
Declaration of interest	None declared	
Notes		
Risk of bias		
bias	author's judgment	support for judgment
Random sequence generation (selection bias)	Unclear risk	No details on random sequence generation were available
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was available

Table 9 (continued)

Blinding of outcome assessment (detection bias)	Unclear risk	No information on blinding of outcome assessors was available
Incomplete outcome data (attrition bias)	Unclear risk	No lost to follow-up or dropouts were reported, but it remains if all patients were evaluated during the analysis for all outcomes
Selective reporting (reporting bias)	Low risk	There is no protocol available. The outcomes listed in the material and methods section of the article are all reported in the results section of the article
Other bias	Unclear risk	Unclear how statistical analysis was performed

RCT, randomized controlled trial.

months, whereas Schmidt et al. [1992] defined a follow-up period of 8 months. Mira et al. [2003] assessed the effects after 3 months. All included studies used one of our prespecified outcome measures (see Types of Outcome Measures).

Vertigo Considering Together Intensity, Frequency, and Duration of Symptoms

All of the included studies included vertigo as one of their outcomes in the follow-up analyses. None of the included studies used the AAO-HNS diagnostic guideline to classify the frequency of vertigo attacks. In 3 studies, the frequency of attacks was used as the main outcome to measure the effect of betahistine after a long-term follow-up (3 months or more), in which all studies used different definitions to quantify the attack frequency, namely the log-transformed number of attacks per 30-day interval based on daily diary reports, the number of vertigo attacks per month, and the imbalance scores based on the number of attacks multiplying the number by 1, 4, or 9 for a mild, moderate, or severe attack, respectively [Schmidt and Huizing, 1992; Mira et al., 2003; Adrion et al., 2016]. Burkin et al. [1967] quantified whether patients experienced dizziness or not, while Elia et al. [1966] based the effect of treatment on a subjective scale, which ranged from 0 to 3. The remaining studies used different ordinal scales to quantify the severity/intensity of the vertigo attacks by means of a 4-point scale [Frew and Menon, 1976], a 5-point scale [Meyer, 1985], a 3-point scale [Okamoto et al. 1968], and a vertigo maximum intensity of the episode and the mean duration of each vertigo episode [Salami et al., 1984]. Ricci et al. [1987] used the AAO classification in which both the effects on vertigo and hearing were combined and classified into 4 groups (A–D).

Significant Adverse Effects: Upper Gastrointestinal Discomfort

The incidence of upper gastrointestinal discomfort was reported by 2 studies [Schmidt and Huizing, 1992; Mira et al., 2003], which both assessed the effect of betahistine in the long term (3 months or more).

Hearing Loss

The effect of betahistine on hearing loss was assessed in 7 studies in variable ways. Adrion et al. [2016] reported results of pure-tone audiometry per frequency (250, 500, 1,000, and 2,000 Hz) and reported the adjusted mean change for placebo; these were compared with the adjusted MD for the low-dose and high-dose betahistine. Frew and Menon [1976] reported the amount of deafness by means of a 4-point scale without any further details. Meyer et al. [1985] reported the mean frequency scores with standard deviation based on the 3-point threshold of 0.5 Hz, 1.0 Hz, and 2.0 kHz. Okamoto et al. [1968] used a 3-point scale by which subjective changes in hearing were assessed. The mean threshold for the frequencies of 0.5, 1.0, and 2.0 Hz were classified by the ANSI in the study of Ricci et al. [1987], resulting in 6 classes (0–25 dB = normal, 26–40 dB = mild hearing loss, 41–55 dB = moderate hearing loss, 56–70 dB = moderately serious hearing loss, 71–90 dB = serious hearing loss, and 91 dB = very serious hearing loss). Salami et al. [1984] used the mean threshold at frequencies of 0.25, 0.5, 1.0, and 2.0 kHz, but no mean and standard deviations were reported. Schmidt and Huizing [1992] used the mean threshold scores based on the frequencies from 0.25 to 2 kHz.

Tinnitus

All but one study reported changes in tinnitus symptoms before and after treatment [Burkin, 1967]. Adrion et al. [2016] used the MiniTF questionnaire, whereas Elia [1966] used a subjective scale that ranged from 0 to 3

Table 10. Schmidt [1992]

Methods	**Study design:** RCT **Study grouping:** crossover
Participants	**Sample size** Number randomized: 40 participants were allocated to either to betahistine or placebo who switched from therapy after a period of 16 weeks, outcomes were measured every month with a total follow-up period of 33 weeks Number completed: 35 participants **Participants baseline characteristics** Age: betahistine 49.5 years (SD 10.1); placebo 49.1 years (SD 7.5) Gender: 24 males (82%) **Unilateral versus bilateral disease**: 27 (77%) **Inclusion criteria:** Complete MD, unilateral or bilateral, according to the Utrecht working definition, that is, cochlear hearing loss, (history of) tinnitus, attacks of vertigo, exclusion of all other diseases that could account for the symptoms. Exacerbation of symptoms during the previous month, for which patients sought medical help; class II **Exclusion criteria:** patients with other otological or general diseases, patients who had undergone surgical treatment for MD, patients who used medication that was likely to influence MD, if this medications had to be continued, patients who were using betahistine dihydrochloride, patients who had experienced side effect of betahistine dihydrochloride – patients with an apparent infection of the middle or the inner ear, with peptic ulcer, bronchial asthma or pheochromocytoma, who were pregnant, suffering from liver or kidney insufficiency, brain tumor, recent head trauma, Parkinson's disease, epilepsy, multiple sclerosis or any other generalized disease, operated upon because of MD, using antihistamines, anti-vertigo drugs, vasodilators, psychotropic drugs or tranquillizers, in case use of these drugs could not be stopped, who had been using betahistine dihydrochloride 3 times 16 mg daily or more for at least the previous 3 months, who had experienced side effect during previous use of betahistine dihydrochloride **Pretreatment:** 1 week with no use of any medication to create a washout effect
Interventions	Intervention group: betahistine dihydrochloride 24 mg 3 times per day, total 72 mg per day with a sustained formula Comparator group: identically appearing placebo capsules 3 times per day Use of additional interventions: not reported
Outcomes	Vertigo was noted as imbalance based on number of attacks, multiplying the number by 1, 4, or 9 for a mild, moderate, or severe attack, respectively The incidence of adverse effects Objective change in hearing loss classified based on the mean hearing thresholds of 0.25–2 kHz Subjective change in tinnitus based on a 4-point scale (none, mild, moderate, severe) Subjective change in aural fullness based on a 4-point scale (none, mild, moderate, and severe) The incidence of other adverse effects
Identification	Sponsorship source: Duphar Nederland B.V. Country: the Netherlands Setting: Outpatient Clinic of Otorhinolaryngology – Head and Neck Surgery, University Medical Centre Utrecht Comments: Author name: J. Schmidt Institution: Otorhinolaryngology – Head and Neck Surgery, University Medical Centre Utrecht Email: not available Address: not available
Declaration of interest	None declared
Notes	

Table 10 (continued)

Risk of bias		
bias	author's judgment	support for judgment
Random sequence generations (selection bias)	Unclear risk	No details on random sequence generation
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was available
Blinding of outcome assessment (detection bias)	Unclear risk	No information on blinding of outcome assessment was available
Incomplete outcome data (attrition bias)	Low risk	Reasons for dropouts described, including an intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcomes listed in the material and methods section of the article are all reported in the results section of the article
Other bias	High risk	Intention-to-treat analysis was not applied because 1 patient crossed over due to side effects earlier than the protocol described, but the data were analyzed per protocol. Follow-up data from dropouts were not accounted for

(3 = incapacitating, 2 = severe, 1 = moderate, 0 = not present). Frew and Menon [1976] used a 4-point scale, Meyer [1985] a 5-point scale, and Okamoto et al. [1968] a 3-point scale. Mira et al. [2003] reported tinnitus as part of the "associated symptoms," which all together were scored with aural fullness, nausea, and vomiting by means of a 4-point scale (0 = absent, 1 = mild, 2 = severe, 3 = disabling). Both Salami et al. [1984] and Ricci et al. [1987] used a scale ranging from 0 to 6, whereas Schmidt and Huizing [1992] used a 4-point scale and the minimum masking level in dB with mean and standard deviations to assess the effect on tinnitus.

Aural Fullness

Aural fullness was reported by 7 of the selected studies, except for Burkin [1967] and Okamoto et al. [1968]. Adrion et al. [2016] reported that participants were instructed to record coexisting symptoms such as aural fullness but data were not shown in the results section. In line with previous outcomes, Frew and Menon [1976] used a 4-point scale and Meyer [1985] a 5-point scale. In line with the tinnitus outcome, Mira et al. [2003] reported aural fullness as part of the "associated symptoms" questionnaire. Both Salami et al. [1984] and Ricci et al. [1987] again used a scale ranging from 0 to 6. Aural fullness was evaluated in Schmidt and Huizing [1992] by means of a scale ranging from none to mild, moderate, or severe, similar to tinnitus.

Other Adverse Effects

The incidence of other adverse effects was reported by 4 studies [Okamoto et al., 1968; Schmidt and Huizing, 1992; Mira et al., 2003; Adrion et al., 2016].

Well-Being and Disease-Specific Health-Related Quality of Life

The effect on well-being was evaluated in 2 studies. Adrion et al. [2016] used the DHI, whereas Mira et al. [2003] used the DHI, the vestibular disorders activities of daily living (VDADL), and the disease-specific health-related quality of life questionnaire.

Excluded Studies

We excluded 13 studies for several reasons: duplicate publication (based on the available information, full texts were checked), wrong study design, wrong comparator, and wrong patient population (see characteristics of excluded studies in tables).

Risk of Bias in Included Studies

Two authors (B.E. and H.Z.-L.) critically reviewed the studies for risk of bias. Where necessary, authors were contacted if we felt more detailed information on the methodology was required. In general, random sequence generation, allocation concealment, and blinding of participant and personnel and outcome assessment were not

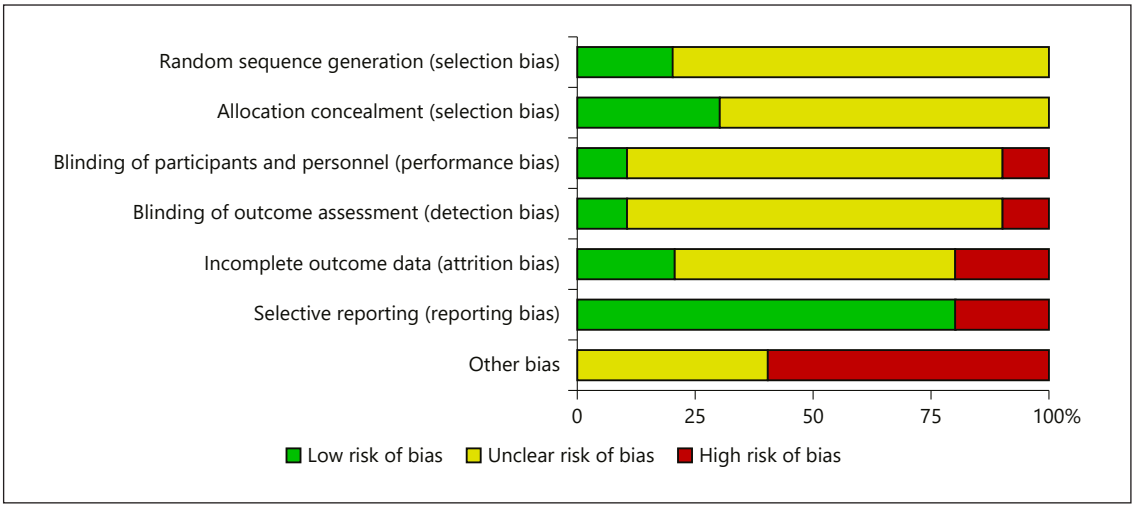


Fig. 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

reported clearly. This can be seen in the number of unclear scores regarding these matters (see Fig. 2). All studies were reported to be double-blinded, whereas only Okamoto et al. [1968] and Adrion et al. [2016] reported in detail how blinding was accomplished. Many studies had incomplete outcome data and other sources of bias, resulting in high risk of bias scores. The characteristics of each trial are listed in the "characteristics of included studies" table, and results on risk of bias are summarized in Figures 2 and 3.

Allocation

Sequence Generation

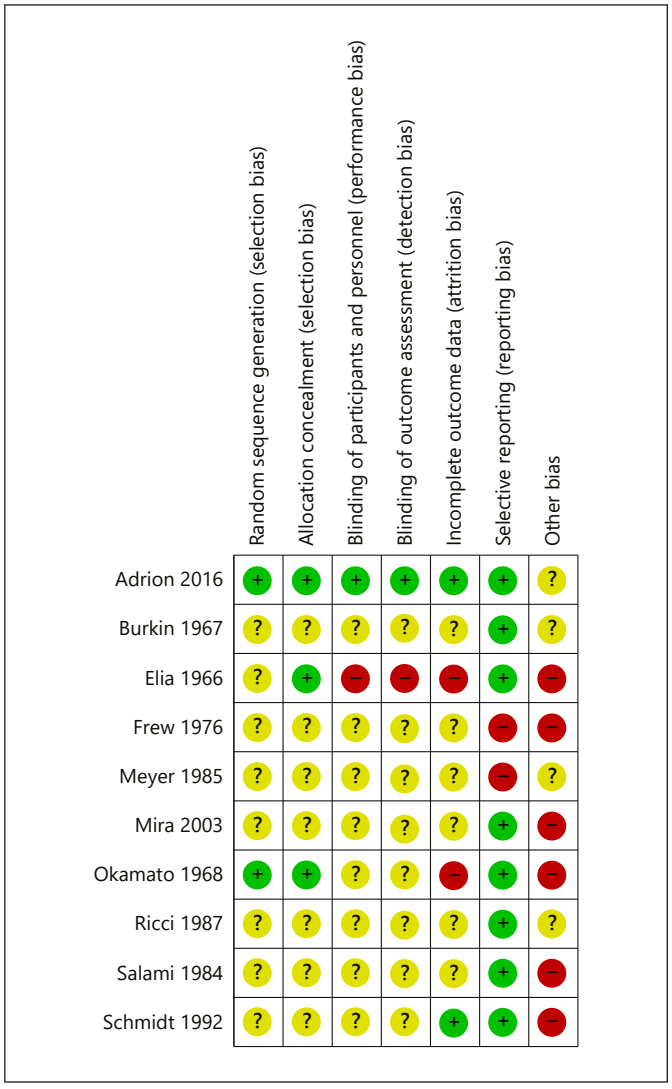
We considered the risk of selection bias due to inadequate method description on sequence generation to be unclear in 7 studies [Elia, 1966; Burkin, 1967; Frew and Menon, 1976; Salami et al., 1984; Meyer, 1985; Schmidt and Huizing, 1992; Mira et al., 2003] and low in the remaining 3 studies [Okamoto et al., 1968; Ricci et al., 1987; Adrion et al., 2016]. In the study performed by Adrion et al. [2016], a 1:1:1 ratio was used, creating a high-dose betahistine, low-dose betahistine, and placebo groups. Okamoto et al. [1968] used a table of random numbers created by a third party independent from the medical institution. Likewise, Ricci et al. [1987] assigned patients to the betahistine or placebo group based on a random list.

Allocation Concealment

The allocation concealment was rated as unclear in all but 3 studies [Elia, 1966; Okamoto et al., 1968; Adrion et al., 2016]. Elia [1966] defined that a fifth person who was not involved in the study coded the tablets. The treating physician, the statistician, the nurse, and the patients were not aware of the given drug, whereas the code was not broken until the final draft of this report. Adrion et al. [2016] described in detail that allocation concealment was performed by means of an Internet-based randomization schedule, which was generated by an investigator with no clinical involvement in the trial. The patients, clinicians, core laboratories, and trial staff were all described as blinded to treatment allocation. Finally, Okamoto et al. [1968] described that drug bottles were labelled with serial number according to the random layout list. The list was created at random by a third party.

Baseline Characteristics

In 2 studies [Elia 1966; Frew and Menon, 1976], no details on baseline characteristics were reported. Both studies were rated as "class III" with regard to the diagnostic criteria applied to include patients with Ménière's disease. Although Okamoto et al. [1968] described the sex distribution among the population, no information on age was given and unclear diagnostic criteria were used to describe the population of studies (class III). With regard to the robustness of diagnostic criteria used to include patients with Ménière's disease, 7 studies were rated as "class III" [Elia, 1966; Burkin, 1967; Okamoto et al., 1968; Frew and Menon, 1976; Salami et al., 1984; Meyer, 1985; Ricci et al., 1987], 2 as "class II" [Schmidt and Huizing, 1992; Mira et al., 2003], and 1 [Adrion et



Color version available online

Fig. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

al., 2016] as "class I." No significant differences were found in the studies that presented baseline characteristics for age and sex distribution [Salami et al. 1984; Ricci et al., 1987; Schmidt and Huizing, 1992; Mira et al., 2003; Adrion et al., 2016]. Only Salami et al. [1984], Ricci et al. [1987], Schmidt and Huizing [1992] and Adrion et al. [2016] reported the duration of disease before the start of the trial. The effect of betahistine on hearing loss was objectively assessed by Salami et al. [1984], Ricci et al. [1987], Schmidt and Huizing [1992], and Adrion et al. [2016], although specific hearing score outcomes were only given by Schmidt and Huizing [1992] and Adrion et al. [2016].

Blinding

Due to inadequate blinding in 7 out of the 9 studies [Elia, 1966; Burkin, 1967; Okamoto et al., 1968; Frew and Menon, 1976; Salami et al., 1984; Meyer, 1985; Ricci et al., 1987; Schmidt and Huizing, 1992; Mira et al., 2003], there was a risk of performance bias and detection bias in most studies. Although Elia [1966] described that a fifth person coded the tablets given during trial execution, the same sequence was repeated (A–D) in all patients. As a result, the intervention could be predicted by the patients, physician, or statistician and was therefore considered to be of high risk. Ricci et al. [1987] described that a random list was used to divide participants, but no information on blinding was provided in the methods section. Therefore, we considered that there was still a considerable risk of inadequate blinding in both studies.

Incomplete Outcome Data

We considered only 2 studies to have a low risk of attrition bias [Schmidt and Huizing, 1992; Adrion et al., 2016], as concrete reasons of non-completion of the trial were given. In the studies performed by Burkin [1967], Frew and Menon [1976], Salami et al. [1984], and Ricci et al. [1987], there was no mentioning of dropping out or discontinuation of trial participation for any reason. But as it remained unclear how many patients were analyzed per outcome and only the level of significance was given, we assessed the risk of attrition bias to be unclear. The risk of attrition bias due to incomplete outcome data was high in Elia [1966], Okamoto et al. [1968], Meyer [1985], and Mira et al. [2003]. In the study performed by Elia [1966], 4 of 20 participants dropped out due to noncompliance to the trial and migration of participants. In 2 patients, it remained unclear whether they had received betahistine or placebo. Meyer [1985] reported a lower number of participants in some outcomes (for instance, disturbed walking pattern) than in other outcomes, but no information was reported on this matter in the manuscript. The participants studied by Mira et al. [2003] were not balanced across groups, for which they did not correct in the analyses. Last, Okamoto et al. [1968] reported that 4 patients out of 36 dropped out (11%), not due to adverse effects of the drug use, but any other reason for dropout was not clarified.

Selective Reporting

A study protocol was available for the study performed by Adrion et al. [2016], published prior to the execution of the study, from which we found that predefined outcomes were evaluated in the published version of the final manu-

script, reporting on study results. In 7 studies, the outcomes that were mentioned in the abstract and/or methods section were also reported in the results section. Therefore, we considered the risk of selective reporting to be low in these studies [Elia, 1966; Burkin, 1967; Okamoto et al., 1968; Salami et al., 1984; Ricci et al., 1987; Schmidt and Huizing, 1992; Mira et al., 2003]. The studies performed by Frew and Menon [1976] and Meyer et al. [1985] mentioned outcomes in the method section that were not shown or described in the results section without reasoning and were considered to suffer from a high risk of selective reporting.

Other Potential Sources of Bias

None of the studies had a low risk bias on other potential sources of bias. Adrion et al. [2016] did not reveal data on pre-randomization attack frequency, although it was considered as an inclusion criterion. Data were not shown with respect to duration and age at the onset of disease, although groups were reported to be balanced based on these characteristics; thus, it remained unclear whether this was performed properly. Although Elia [1966], Burkin [1967], Salami et al. [1984], Meyer [1985], and Ricci et al. [1987] reported no details on how statistical analysis was performed, the authors concluded that a positive effect of betahistine on symptoms of Ménière's disease was found; this was considered to be a high potential source of bias [Elia, 1966; Burkin, 1967; Salami et al., 1984; Meyer, 1985; Ricci et al., 1987]. Frew and Menon [1976] used 1-sided testing, which should have been 2-sided. Moreover, standard deviations were not reported, and we considered a high risk of selection bias due to a pretreatment period, in which the investigator was allowed to exclude placebo responders, thereby decreasing external validity of the study results. Sample size calculation performed by Mira et al. [2003] was done without referring to previous studies performed. In the outcome section, improvement of associated symptoms including tinnitus, fullness of the ear, nausea, and vomiting was summarized in 1 figure. However, it was unclear how it was performed and whether data were complete. The trial medication during the execution of the trial by Okamoto et al. [1968] was supplied by Eisai Co.; the role of this subsiding party remained unclear. We considered there was a high risk of bias in the study by Schmidt and Huizing [1992] since the intention-to-treat analysis was not correctly executed because 1 patient crossed over due to side effects earlier than the protocol stated. Furthermore, the data were analyzed per protocol. Moreover, in these analyses, the authors did not account for the loss of follow-up from dropouts.

Results

The effects of the interventions are summarized in Table 11 (summary of findings).

Primary Outcomes

Proportion of Patients with a Reduction in Vertigo Symptoms (Considering Together the Intensity, Frequency, and Duration of Those Symptoms)

All of the included studies evaluated the effect of betahistine on vertigo symptoms by means of different Likert-type scales or by using a mathematical formula, resulting in both dichotomous and continuous data; we therefore could not pool the data for this outcome. In addition, data from the first period could not be extracted from 4 crossover studies [Elia, 1966; Burkin, 1967; Frew and Menon, 1976; Meyer, 1985]. Ricci et al. [1987] combined the effect on vertigo and hearing loss to 1 outcome, and no numerical data were presented. No data could be extracted from Salami et al. [1984].

Short-Term Follow-Up (<3 Months)

Okamoto et al. [1968] used a 3-point visual analog scale, from which the proportion of patients with an improvement in vertigo symptoms at short-term follow-up was quantified. The RR was 3.0 (95% confidence interval [CI] 0.97–9.30) in favor of betahistine (GRADE: low certainty) (Fig. 4).

Long-Term Follow-Up (>3 Months)

Schmidt and Huizing [1992], Mira et al. [2003], and Adrion et al. [2016] all assessed the effect of betahistine after a long-term follow-up. Data could not be pooled because there was significant heterogeneity in outcomes between studies and no raw data to impute standard deviations were available. Mira et al. [2003] described a significant improvement in the monthly vertigo attack frequency without presenting absolute baseline and endpoint data for the placebo group. Schmidt and Huizing [1992] found no difference between the betahistine and placebo groups in the effect on imbalance scores. The study of Adrion et al. [2016] was the study with the lowest risk of bias; this study found no favorable effect after comparing high-dose and low-dose betahistine to placebo. In summary, 2 studies found no favorable effect for betahistine, which included 1 study with a high quality [Schmidt and Huizing, 1992; Adrion et al., 2016]. We assessed the certainty of the evidence for this outcome as moderate (GRADE).

Table 11. Summary of findings

Betahistine compared with placebo for Ménière's disease or syndrome						
Patient or population: Ménière's disease Setting: outpatient clinics Intervention: betahistine Comparison: placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Participants, *n* (studies)	Quality of the evidence (GRADE)	Comments
	placebo	betahistine				
Vertigo considering together intensity, frequency, and duration of symptoms measured by a visual analog scale (range 0–5, questionnaire) Follow-up: up to 3 months	Study population **167 per 1,000**	**500 per 1,000**	**RR 3.00** (0.97–9.30)	36 (1)	⊕⊕◯◯ Low[1]	Nonsignificant difference between groups. If 1,000 patients are treated with betahistine, 333 more will have an improvement in vertigo than if they had taken placebo alone
Vertigo considering together intensity, frequency, and duration of symptoms (range 30-day interval vertigo rate, imbalance scores) Follow-up: up to 9 months	Study population		Not estimable	259 (3)	⊕⊕⊕◯ Moderate[2]	Two studies out 3 studies found no significant difference between treatment with betahistine and placebo, including 1 high-quality trial
Significant adverse effect (upper gastrointestinal discomfort [yes or no]) Follow-up: up to 33 weeks	Study population **86 per 1,000**	**83 per 1,000**	**RR 0.86** (0.13–5.83)	37 (1)	⊕⊕◯◯ Low[3]	Nonsignificant difference between groups. If 1,000 patients are treated with betahistine, 3 fewer will have a significant adverse effect than if they had taken placebo
Hearing loss (improved: yes or no) Follow-up: up to 2 weeks	Study population **56 per 1,000**	**167 per 1,000**	**RR 3.0** (0.34–26.19)	36 (1)	⊕⊕◯◯ Low[1]	Nonsignificant difference between groups. If 1,000 patients are treated with betahistine, 111 more will have an improvement in hearing loss than if they had taken placebo
Hearing loss (improved: yes or no) Follow-up: for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment	Study population **0 per 1,000**	**200 per 1,000**	**RR 3.0** (0.15–59.89)	10 (1)	⊕◯◯◯ Very low[4]	Nonsignificant difference between groups. If 1,000 patients are treated with betahistine, 200 more will have an improvement in hearing loss than if they had taken placebo
Hearing loss (measured by the adjusted mean change presented per frequency; mean hearing thresholds of 0.25–2 kHz) Follow-up: up to 9 months	The mean hearing loss score was 47.8 in the control group	The mean hearing loss score was 9.9 dB higher in the intervention group	**MD 10.10** (−0.97, 21.17)	35 (1)	⊕⊕◯◯ Low[3]	Nonsignificant difference between groups, mean hearing loss score was 9.9 dB higher in the betahistine group
Tinnitus (improved: yes or no) Follow-up: up to 12 weeks	Study population **167 per 1,000**	**444 per 1,000**	**RR 2.67** (0.84–8.46)	36 (1)	⊕⊕◯◯ Low[1]	Nonsignificant difference. If 1,000 patients are treated with betahistine, 277 more will have an improvement in tinnitus than if they had taken placebo

Table 11 (continued)

Tinnitus (improved: yes or no) Follow-up: for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment	Study population **1,000 per 1,000**	**1,000 per 1,000**	**RR 1.00** (0.71–1.41)	10 (1)	⊕◯◯◯ Very low[4]	Nonsignificant difference. If 1,000 patients are treated with betahistine, no difference will be seen in the effect on tinnitus compared to if they had taken placebo
Tinnitus measured by the MiniTF questionnaire Follow-up: up to 9 months	The adjusted mean change was 0.67 (−0.049 to 0.182)	The adjusted treatment difference (95% CI) was 0.016 (−0.0147 to 0.114) lower in the high-dose betahistine group	**MD −0.16** (−0.48 to 0.17)	144 (1)	⊕⊕⊕◯ Moderate[2]	No significant difference between betahistine and placebo was seen on tinnitus, as measured by the MiniTF questionnaire
Other adverse effects (yes or no) Follow-up: up to 3 months	Study population **167 per 1,000**	**278 per 1,000**	**RR 1.67** (0.47–5.96)	36 (1)	⊕⊕◯◯ Low[1]	Nonsignificant difference. If 1,000 patients are treated with betahistine, 111 more will have others adverse effects than if they had taken placebo
Other adverse effects (yes or no) Follow-up: up to 9 months	Study population **61 per 1,000**	**165 per 1,000**	**RR 2.58** (1.21–5.49)	265 (3)	⊕⊕⊕◯ Moderate[5]	Significant difference. If 1,000 patients are treated with betahistine, 104 more will have others adverse effects than if they had taken placebo
Well-being and disease-specific quality of life based on visual analog scale (3-point scale with 3 domains) Follow-up: 9 months	The adjusted mean change (95% CI) was −1.04 (−0.353 to 0.145)	The adjusted treatment difference (95% CI) was 0.025 (−0.267 to 0.217) lower in the high-dose betahistine group	**SMD 0.08** (−0.25–0.40)	144 (1)	⊕⊕⊕◯ Moderate [2]	Nonsignificant difference. The adjusted treatment difference was 0.025 lower in the high-dose betahistine group

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

CI, confidence interval; RR, risk ratio; MD: mean difference; SMD: standardized mean difference. * The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [1] Downgraded 1 level due to the use of non-validated outcome measures; downgraded 1 level due to imprecision. [2] Downgraded 1 level due to the use of non-validated outcome measures. [3] Downgraded 1 level due to study limitations (unclear risk of bias for sequence generation, allocation concealment, and blinding); downgraded 1 level due to the level of uncertainty of the diagnosis (use of class II diagnostic criteria). [4] Downgraded 1 level due to study limitations (unclear risk of bias for sequence generation, allocation concealment, and blinding); downgraded 1 level due to the level of uncertainty of the diagnosis (use of class III diagnostic criteria); downgraded 1 level due to imprecision. [5] Downgraded 1 level due to inclusion of patients with a level of uncertainty of the diagnosis (use of class II diagnostic criteria).

Significant Adverse Effect: Upper Gastrointestinal Discomfort

Both Schmidt and Huizing [1992] and Mira et al. [2003] reported no significant difference in the incidence of upper gastrointestinal discomfort. The pooled RR was 0.86 (95% CI 0.13–5.83; 2 studies; 118 participants) in favor of placebo (Fig. 5) (GRADE: low certainty).

Secondary Outcomes

Hearing Loss

Hearing loss was evaluated in both the short and long term by means of both dichotomous data (proportion of patients with improvement) [Okamoto et al., 1968; Ricci et al., 1987] and continuous data based on means with corresponding 4-point thresholds for the frequencies from 0.25 to 2.0 kHz [Schmidt and Huizing, 1992]. Data

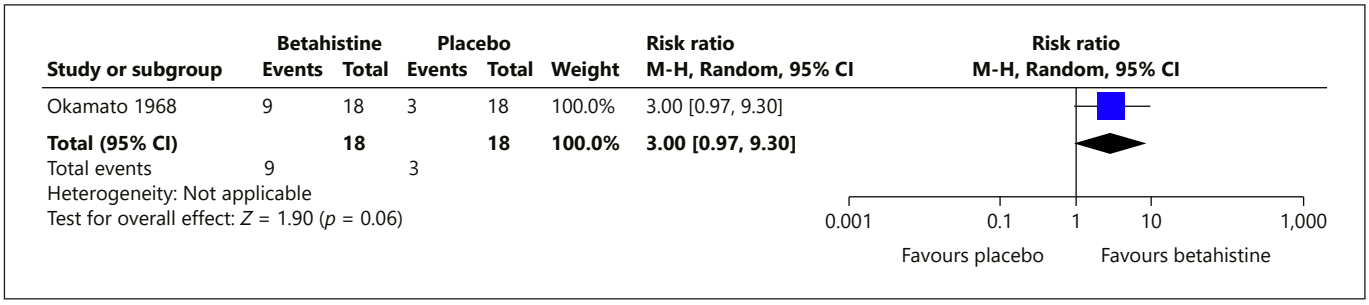


Fig. 4. Outcome on vertigo considering together intensity, frequency, and duration of symptoms (short term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of <3 months. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

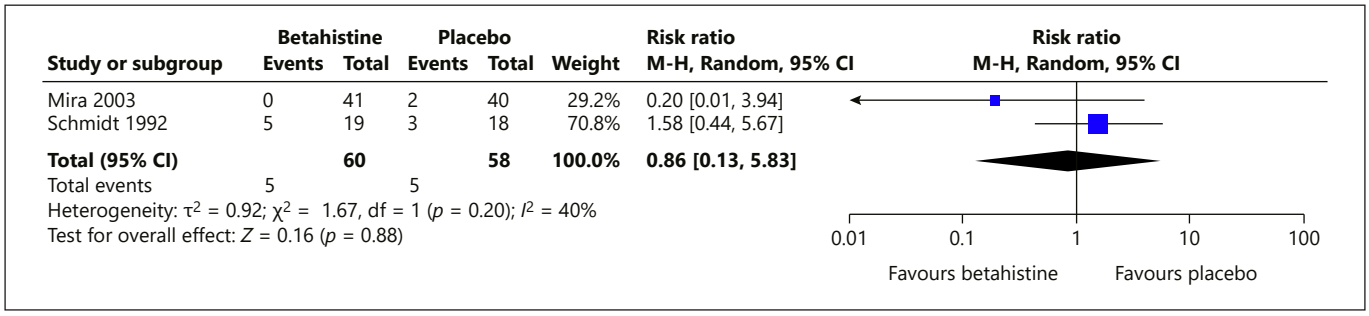


Fig. 5. Outcome on significant adverse effects (long term), with comparison between betahistine and placebo. The filled squares represent the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

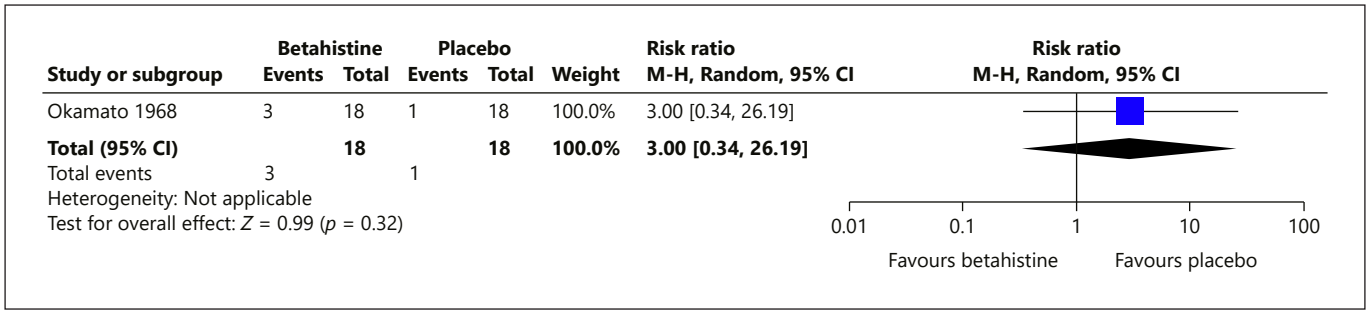


Fig. 6. Outcome on hearing loss (short term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of <3 months. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

from the 4 remaining studies could not be pooled because only data per frequency were reported and no mean 4-point threshold score could be calculated [Adrion et al., 2016], no pre-crossover data were available [Frew and Menon, 1976; Meyer, 1985], or no data were presented [Salami et al., 1984]. No significant difference between the betahistine and placebo groups could be found in the included studies.

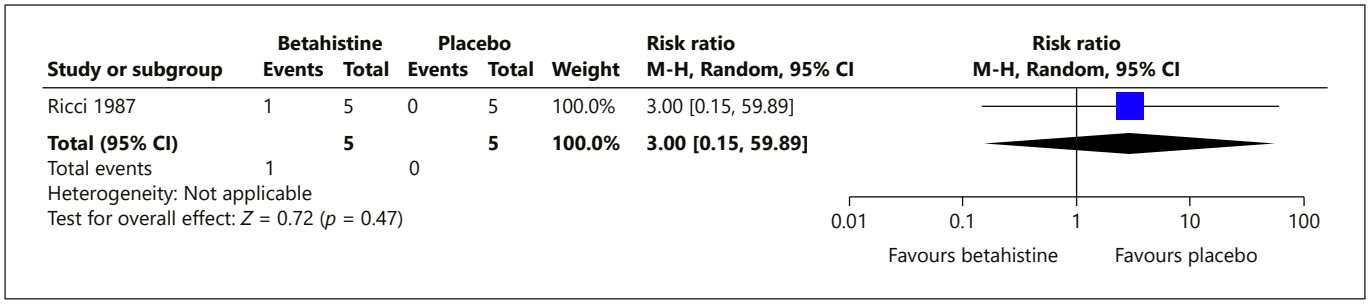


Fig. 7. Outcome on hearing loss (long term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

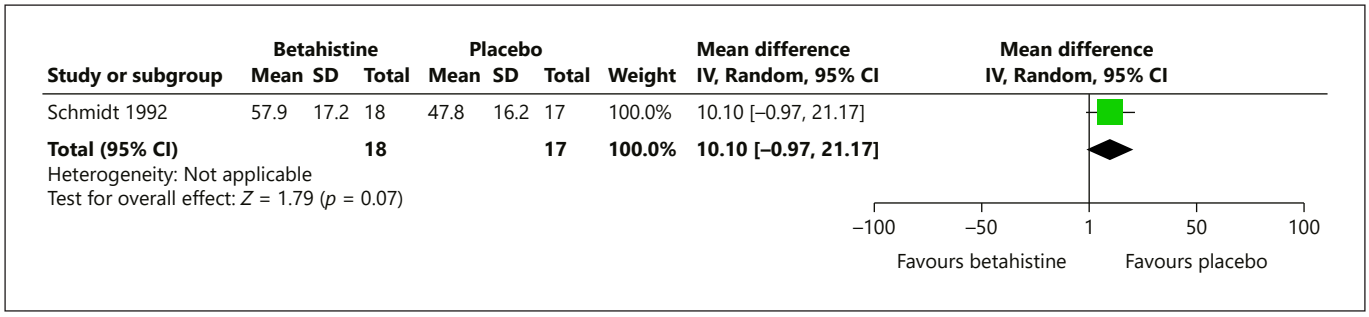


Fig. 8. Pooled outcome on hearing loss (long term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of <3 months. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

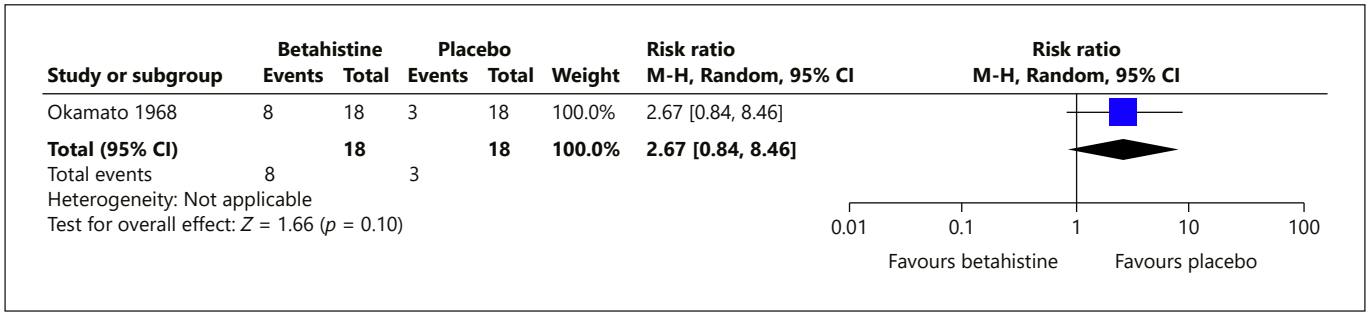


Fig. 9. Outcome on tinnitus (short term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of <3 months. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

Short-Term Follow-Up (<3 Months)

In the short term, Okamoto et al. [1968] reported an RR of 3.00 (95% CI 0.34–26.19; 1 study; 36 participants) for the improvement of hearing (GRADE: low certainty) (Fig. 6).

Long-Term Follow-Up (>3 Months)

The long-term effect on hearing loss was evaluated by Ricci et al. [1987], which reported an RR of 3.00 (95% CI 0.15–59.89; 1 study; 10 participants) (GRADE: very low certainty) (Fig. 7). Schmidt and Huizing [1992] found no

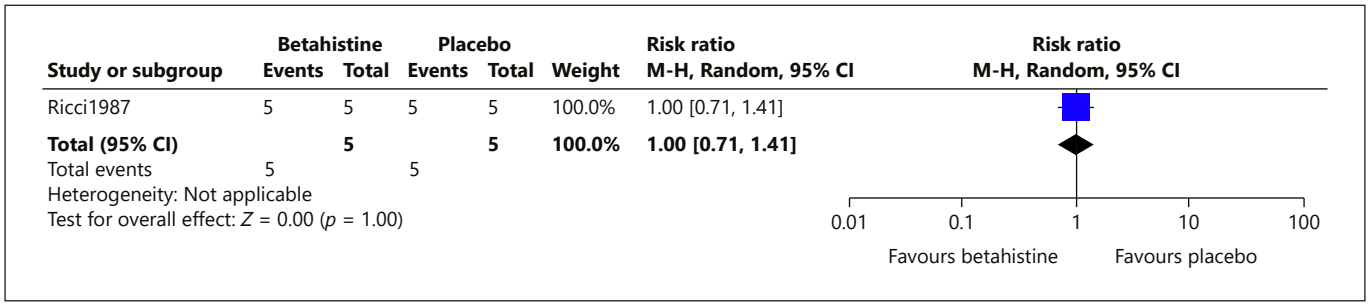


Fig. 10. Outcome on tinnitus (long term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

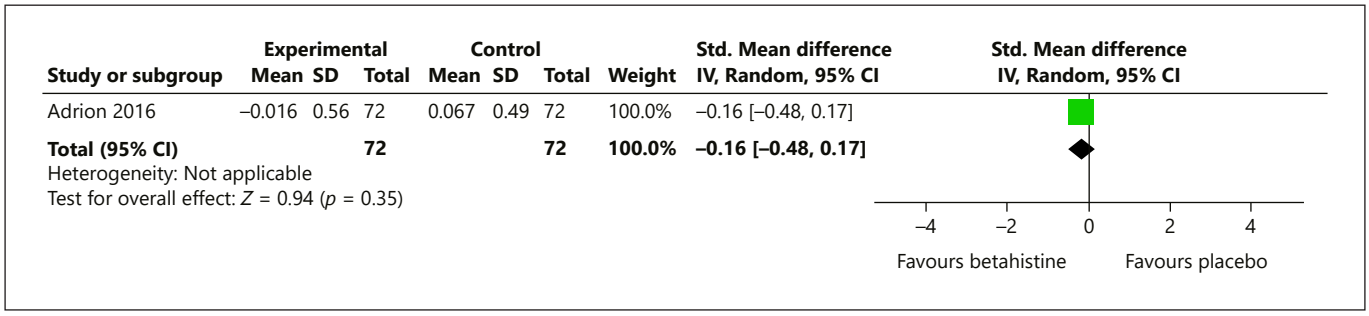


Fig. 11. Outcome on tinnitus (long term), with comparison betahistine versus placebo. The filled square represents the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

difference between the betahistine group and the placebo group based on mean threshold scores at long-term follow-up (MD 10.10, 95% CI −0.97 to 21.17; 1 study; 35 participants) (GRADE: low certainty) (Fig. 8).

Tinnitus

Short-Term Follow-Up (<3 Months)

The effect of betahistine on tinnitus was evaluated at short-term follow-up by Okamoto et al. [1968], which reported the proportion of participants with an improvement in RR of 2.67 (95% CI 0.84–8.46; 1 study; 36 participants) (GRADE: low certainty) (Fig. 9). These results are not statistically significant or clinically relevant.

Long-Term Follow-Up (>3 Months)

At long-term follow-up, Ricci et al. [1987] found no difference between the betahistine group and the placebo group based on the proportion of patients without deterioration of hearing (RR 1.00, 95% CI 0.71–1.41; 1 study; 10 participants) (GRADE: very low certainty) (Fig. 10). Long-term effect was reported as the SMD based on the MiniTF in Adrion et al. [2016], which found no difference between betahistine and placebo groups (SMD −0.16, 95% CI −0.48 to 0.17; 1 study; 144 participants) (GRADE: moderate certainty) (Fig. 11).

Aural Fullness

Data on aural fullness could not be extracted from any of the 7 studies because first period, pre-crossover data could not be extracted [Frew and Menon, 1976; Meyer, 1985], no aural fullness data were presented [Adrion et al., 2016], no numerical data were presented [Salami et al., 1984; Schmidt and Huizing, 1992], data for the betahistine group and placebo group were not shown [Ricci et al., 1987], or results were reported only with a *p* value without data on baseline absolute values and endpoint values [Mira et al., 2003].

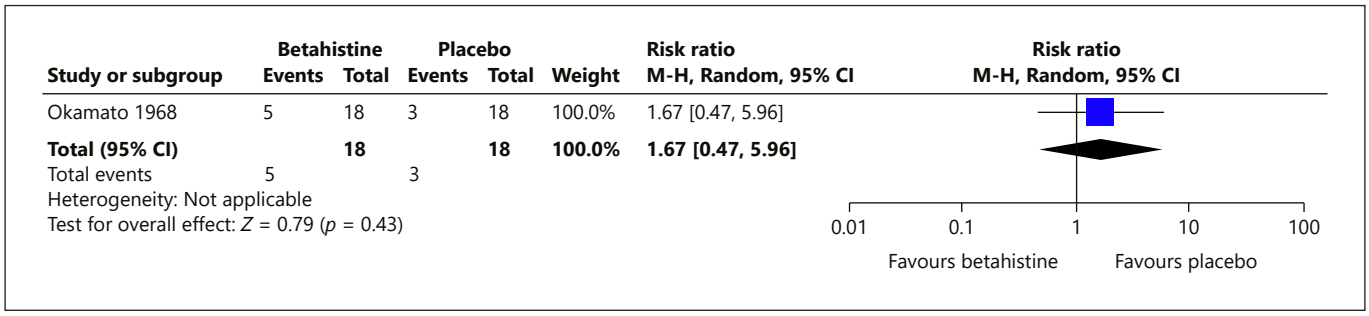


Fig. 12. Outcome on other adverse effects (long term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

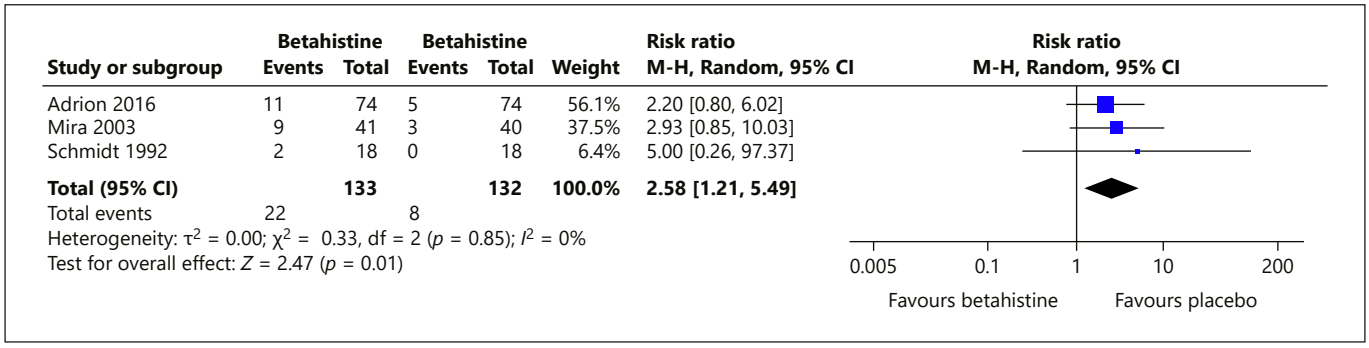


Fig. 13. Outcome on other adverse effects (long term), with comparison between betahistine and placebo. The filled squares represent the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

Other Adverse Effects

The incidence of "other" adverse effects was reported at both short and long-term follow-up, which were dull headache, tinnitus, ear discomfort, nervous system disorders, headache, heart burn, skin rash, increased diuresis, extrasystoles, and oral formication.

Short-Term Follow-Up (<3 Months)

Okamoto et al. [1968] found no significant difference in other adverse effects between the betahistine and placebo groups (RR 1.67, 95% CI 0.47–5.96; 1 study; 36 participants) (GRADE: low certainty) (Fig. 12).

Long-Term Follow-Up (>3 Months)

At long-term follow-up, Schmidt and Huizing [1992], Mira et al. [2003], and Adrion et al. [2016] found a lower RR in favor of placebo than for betahistine. The pooled RR was 2.58 (95% CI 1.21–5.49; 3 studies; 265 participants) (GRADE: moderate certainty) (Fig. 13).

Well-Being and Disease-Specific Health-Related Quality of Life

Disease-specific health-related quality of life was evaluated by Mira et al. [2003], but because the results were reported only as percentage reductions without baseline absolute values and missing measures of spread, no useful data could be extracted. Adrion et al. [2016] evaluated disease-specific health-related quality of life by means of the DHI, which was reported as SMDs compared to placebo. No significant difference between the placebo and high-dose betahistine group could be demonstrated (SMD 0.08, 95% CI −0.25 to 0.40; 1 study; 144 participants) (GRADE: moderate certainty) (Fig. 14).

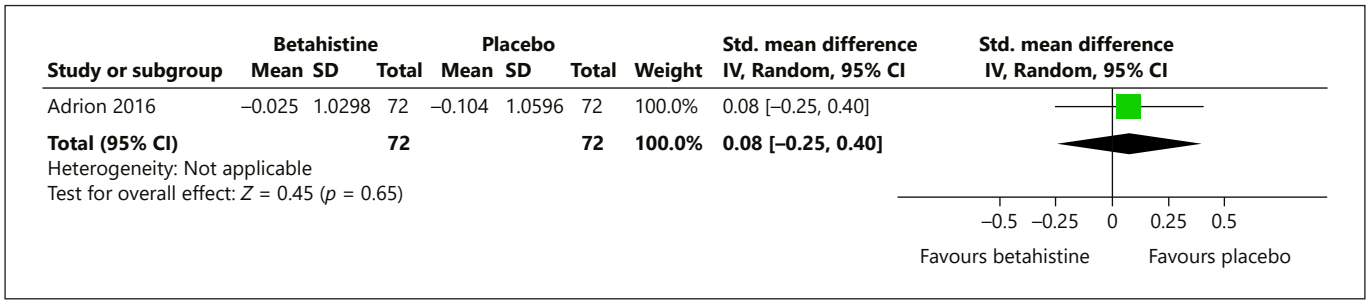


Fig. 14. Outcome on well-being and disease-specific quality of life (long term), with comparison between betahistine and placebo. The filled square represents the RR for individual studies with a follow-up of 3 months or more. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% CI. The filled diamond represents the pooled RR (if applicable), and its width represents its 95% CI. RR, risk ratio; CI, confidence interval.

Discussion

Summary of Main Results

The current review includes 10 RCTs, which evaluated the effects of betahistine compared to placebo in a total of 402 adult participants with Ménière's disease. For the primary outcome, the reduction in vertigo symptoms (considering together the intensity, frequency, and duration of those symptoms), there was clinical heterogeneity between studies due to differences in the outcome measured and methods used. We could, therefore, not perform data pooling for this outcome. One adequately powered study with low risk of bias did not find evidence of a difference between the betahistine and placebo groups for this outcome [Adrion et al., 2016]. We assessed the certainty of this evidence to be moderate (GRADE). No statistically significant or clinically relevant difference was found with respect to the significant adverse effect (upper gastrointestinal discomfort) in the 2 studies that reported this outcome [Schmidt and Huizing, 1992; Mira et al., 2003]. No differences in hearing loss, tinnitus, or well-being and disease specific health-related quality of life were found between the betahistine and placebo groups in any of the individual studies assessing these outcomes (low- to very low-certainty evidence). Aural fullness was evaluated by 1 study based a non-validated visual analog scale, which lacked information whether or not results were statistically better in the betahistine than in the placebo group. The other adverse effect that was seen in the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effects in the long term included tinnitus, ear discomfort, nervous system disorders, headache, heartburn, skin rash, increased diuresis, extrasystoles, and oral formication. The pooled RR demonstrated a lower risk in favor of placebo over betahistine. High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, 1 study with low risk of bias found no evidence of a difference in the effect of betahistine on the primary outcome, vertigo, in patients with Ménière's disease when compared to placebo [Adrion et al., 2016].

Overall Completeness and Applicability of Evidence

Specific diagnostic criteria were used to select patients for trial participation in only one of the included studies [Adrion et al., 2016]. In the remaining studies, either rather vague diagnostic criteria were applied, including recruiting patients with "probable" Ménière's disease, or no details were provided about how patients were diagnosed with Ménière's disease. In particular, in the 6 studies involving "class III" rated participants (see Types of Participants), it remains disputable whether these patients can be considered to have Ménière's disease. The applicability of the evidence in these studies is therefore limited. In none of the included studies were data provided on the previous duration of the disease, including the frequency and intensity of attacks. Generally, in Ménière's disease, vertigo attacks stop after approximately 5–15 years. It is, therefore, of great importance that this information is collected before trials are started to allow the interpretation of any observed treatment effect.

Quality of the Evidence

The certainty of the evidence in this review ranged from moderate to very low, although 1 high-quality study was included [Adrion et al., 2016]. Since none of the studies used similar methods to evaluate the effect of treatment on vertigo, it remains hard to assess whether the reported estimates are true. Future research should aim

to use more standardized and comparable methods to assess the effect on vertigo in order to increase the level of evidence and allow more concrete conclusions to be drawn from the data. The certainty of the evidence was mainly negatively affected by study limitations (risk of bias of bias), the low level of external validity, and imprecision due to the small sample sizes. Studies lacked information on the selection procedure used to identify participants, and methods were poorly reported, especially with respect to statistical analyses. In most studies, it remained unclear how randomization, allocation concealment, and blinding of personnel, participants, and outcome assessors were performed. Only one of the included studies had a prepublished protocol available for inspection.

Potential Biases in the Review Process

We made no significant changes to our planned methods. We performed a comprehensive electronic database search. Language was not a barrier for inclusion, and we reviewed full-text articles in Japanese, German and Italian after these were translated. The roles of all authors were predefined before the start of the review process. Two authors selected studies for inclusion and judged risk of bias independently. Two authors independently extracted data to minimize personal bias. Both clinical and statistical heterogeneity were evaluated before considering quantitative analyses. The predefined outcome measures were as broad as possible, aiming to allow the summarizing of data or make pooling of data more feasible.

Agreements and Disagreements with Other Studies or Reviews

At least 2 other reviews have evaluated the effect of betahistine in the treatment of Ménière's disease [Lacour et al., 2007; Nauta, 2013]. Both reviews concluded that there is a favorable effect of betahistine on vertigo. Lacour et al. [2007] is an expert opinion paper, which describes the definition of Ménière's disease and its epidemiology and pathophysiology and the role of betahistine in its therapeutic management including the mechanisms of action, which are hypothesized to play a role in the potential positive effect of the drug. The favorable clinical effect of betahistine is evaluated by means of a narrative summary of the results found in the study of Mira et al. [2003]. In addition, comparative studies and the results of an as yet unpublished open trial study are discussed. No data pooling or meta-analysis was performed. The authors concluded that betahistine is an effective therapy for Ménière's disease and related conditions. Nauta et al. [2013] is a review and meta-analysis on patients with vestibular vertigo or Ménière's disease, which aimed to assess the "overall judgment of the investigator on the effectiveness of the drug treatment." Statistical analyses were performed to combine ordered categorical data. The overall random effect, the average odds ratio, was 2.58 (95% CI 1.67–3.99). When restricted sub-analyses of Ménière's disease patients only were performed, the average odds ratio was 3.37 (95% CI 2.14–5.29). No analysis of validity or risk of bias assessment was presented. Cochrane ENT has published 2 systematic reviews evaluating the effects of betahistine for other clinical indications than Ménière's disease. One review evaluated the effect of betahistine on symptoms of vertigo, identifying 17 studies (1,025 participants) [Murdin et al., 2016]. Out of these 17 studies, 5 evaluated the effect of betahistine for Ménière's disease, from which the pooled RR was 1.56 (95% CI 0.92–2.62; 3 studies; 139 participants). Similar to the current review, the authors stated that results need to be interpreted with caution, as the diagnoses differed between studies and did not necessarily meet the standard diagnostic criteria. Moreover, the incidence of adverse effects was similar for both betahistine and placebo groups. The second review evaluated the effect of betahistine on tinnitus and included 5 studies (303–305 participants) [Wegner et al., 2018]. This review concluded that there is no evidence to suggest that betahistine has an effect on subjective idiopathic tinnitus.

Recently, a clinical practice guideline for Ménière's disease was published, which includes an advice concerning oral pharmacotherapy [Basura et al., 2020]. Both diuretics and betahistine are mentioned as an optional treatment. The guideline mentions that serious side effects are rare and patients should be clinically reassessed to monitor improvement and intolerance of side effects. In case the symptoms may subside, it is advised to titrate down or stop its use. We believe that it is of great importance that patients should be informed about the lack of efficacy found in the study by Adrion et al. [2016], since this study offers the best evidence to date. Nonetheless, periodic clinical evaluation regarding the effects, intolerance, or side effects may help patients and clinicians in their decision to either stop or continue treatment with betahistine.

In summary, previous reviews have concluded either that there is insufficient evidence to say whether betahistine has any effect on Ménière's disease or that there may be a positive effect of betahistine based on low-quality studies, so further research is likely to have an important

impact on the interpretation of the results. In line with the findings of the current review, previous work has also concluded that betahistine is generally well tolerated with a similar risk of treatment-related adverse effects to placebo. Moreover, all previously evaluated studies included in reviews or meta-analyses have suffered from significant heterogeneity with respect to participants, dose of betahistine, follow-up duration, and the methods of evaluation for outcomes.

Conclusions

Implications for Practice

High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, 1 study with high quality found no evidence of a difference in the effect of betahistine on the primary outcome, vertigo, in patients with Ménière's disease when compared to placebo [Adrion et al., 2016]. Betahistine appears to be generally well tolerated, and the risk of gastrointestinal discomfort is comparable to that of placebo. Further studies with a low risk of bias (in particular, with respect to allocation and blinding) and rigorous inclusion criteria are required to independently verify the lack of evidence of a beneficial effect of betahistine for Ménière's disease compared to placebo. Patients considering treatment options should be informed about the findings of this review, which found no evidence of a beneficial effect of betahistine on the primary outcome, vertigo. Patients should also be informed that betahistine is generally well tolerated and the risk of adverse effects is low and comparable to that of placebo. Based on this information, patients may still choose to start their treatment with betahistine, especially in the current absence of any other safe, noninvasive effective treatment that has high patient acceptability and relatively low cost and is well supported by high-certainty evidence. Nonetheless, it remains questionable whether prescription of betahistine is justifiable or cost-effective. If patients decide to proceed with betahistine, a trial period of around 3 months could be offered. This period is sufficient to assess whether the patient experiences any beneficial effects on their symptoms or any adverse effects. If any unwanted effects outweigh any benefit, or there is no apparent improvement, therapy can be withdrawn.

Implications for Research

Future research into the effectiveness of betahistine in patients with Ménière's disease should use rigorous methodology. Due to the subjective nature of most outcome measures, the risk of bias with respect to randomization and blinding needs to be low to avoid any placebo effect. Standardized diagnostic criteria should be rigorously applied. A standardized method of designing and reporting trial results such as the CONSORT statement should be used (CONSORT 2010). We recommend validated, patient-centered outcome measures for research in the field of Ménière's disease. A core outcome set would be of particular value for this condition because of the multiple subjective symptoms that are characteristic. By means of a core outcome set, a standardized set of outcomes would be reported, which would facilitate direct comparison between studies and the ability to perform data pooling. Due to the highly variable and poorly understood natural history of Ménière's disease, baseline characteristics and information on the natural course of the disease is of great importance for the interpretation of the treatment effects. For instance, information on the duration of disease, the frequency of vertigo attacks since the start of the disease, the duration and intensity of the vertigo attacks, age, and the amount of hearing loss may all be of value at the time of trial enrolment. Moreover, with the exception of the 1 high-quality study [Adrion et al., 2016], none of the included studies in this review carried out an adequate power calculation before the start of trial. Future trials should include a power analysis to make sure that the estimated difference in effect between treatment arms can indeed be identified by the number of included participants. Research into the natural history of the condition via prospective longitudinal studies or registries would also be valuable in planning future clinical trials of therapy for Ménière's disease. However, in the light of limited means; the huge effort involved in conducting a trial on the part of patients, doctors, and researchers; and the very low estimated added value of betahistine in the treatment of Ménière's disease found in this review, we anticipate that research on this topic may not be prioritized.

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Statement of Ethics

The paper is exempt from Ethical Committee approval since it involves analyses on previously published data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors were involved in the drafting of the protocol. B.E. selected and obtained studies, extracted data, and assessed risk of bias. B.E. entered data into RevMan 5 and carried out and interpreted the analyses. B.E. drafted the final review and has responsibility for updating and maintaining the review. H.Z.-L. selected studies, extracted data, assessed risk of bias, and helped interpret the analyses. H.Z.-L. provided advice throughout the analyses and drafted the final review. T.B. provided advice and drafted the final review. P.P.B. initiated the revision of the review, provided advice, and drafted the final review.

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