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Menière's disease: Clinical aspects, diagnostic tests and interventions

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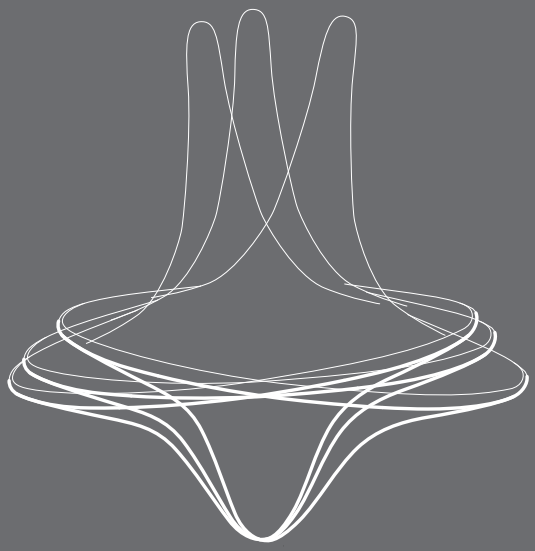

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BETAHISTINE IN MENIÈRE'S DISEASE OR SYNDROME: A SYSTEMATIC REVIEW

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Submitted

BACKGROUND

Menière's disease is characterised 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. To date, clinical therapy options include dietary modifications, intratympanic injections with methylprednisolone, dexamethasone or gentamicin, positive pressure therapy, endolymphatic sac decompression, endolymphatic duct blockage, ablative surgery such as vestibular nerve section or surgical labyrinthectomy and oral administration of betahistine. Betahistine dihydrochloride is an oral drug that has been prescribed to an estimated 130 million people worldwide since its first launch. Although betahistine has been used for vestibular vertigo in general it is thought by some clinicians to be specifically effective for Menière's disease. Nonetheless, no evidence for a benefit from the use of betahistine, despite its widespread use, especially in Europe. Reassessment of the effect of betahistine in the treatment of Menière's disease is therefore now warranted.

Objectives: To assess the effects of betahistine in patients with Menière disease or syndrome.

Search methods: Were performed by the Cochrane Ear, Nose and Throat Disorders Group (CENTDG) Information Specialist searched the Cochrane ENT Register; 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Ovid Medline; Ovid Embase; CINAHL; Web of Science; Clinicaltrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 16 January 2018 which was re-run on 29 January 2019.

Selection criteria: Randomised controlled trials (RCTs) evaluating patients with Menière's disease. We included studies in which the intervention involved betahistine and was compared to placebo. We evaluated all courses of betahistine: any dose regimes or formulations and for any duration of treatment.

Data collection and analysis: We used the standard methodological procedures expected by Cochrane. Our primary outcomes involved vertigo and significant adverse effect (upper gastrointestinal discomfort). Our secondary outcomes included hearing loss as measured by a pure-tone audiogram based on the four-tone average of thresholds at 0.5 kHz, 1 kHz, 2 kHz and 3 kHz, tinnitus measured by patient-reported questionnaire scores, aural fullness measured by patient-reported questionnaire scores, other adverse effects (headache and allergic skin reactions (pruritus, rashes)), and well-being and disease-specific health-related quality of life. We used GRADE to assess the quality of the evidence for each outcome.

Main results: We included 10 studies with a total of 402 participants. Four studies used a cross-over design and the remaining five were parallel-group RCTs. All studies were conducted in otorhinolaryngology departments within hospitals in Europe, the USA and Japan. All participants were adults with Ménière's disease, but different inclusion criteria and definitions for the disease were used. The daily dose of betahistine ranged between 16 mg and 144 mg. The risk of bias was unclear or high in all but one of the studies.

Primary outcomes: Although all of the included studies evaluated the effect of betahistine on vertigo, data pooling was not possible because of the heterogeneity in the evaluated participants and the lack of information about how they were diagnosed, the outcomes measured and the measurement methods used. One study with low risk of bias found no significant difference between the betahistine groups and placebo with respect to reduction in vertigo symptoms after a long-term follow-up period (more than three months). Two studies reported no significant difference in the incidence of upper gastrointestinal discomfort (low-certainty evidence).

Secondary outcomes: 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 of evidence). Data on aural fullness could not be extracted from any of the studies.

The other adverse effect that was seen on the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effect on the long term included tinnitus, ear discomfort, nervous system disorders, headache, heartburn, skin rash, increased diuresis, extrasystoles and oral formication. The pooled risk ratio demonstrated a lower risk in favour of placebo over betahistine.

Authors' 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. Betahistine appears to be generally well tolerated and the risk of adverse effects on upper gastrointestinal discomfort is comparable to that of placebo. The main focus of future research should be on the use of comparable outcome measures across studies in order to increase homogeneity and therefore enable data pooling. This could be done by means of patient-reported outcome measures that have been developed and are used in other medical fields. A standardised method of designing and reporting trial results should be used, such as CONSORT.

PLAIN LANGUAGE SUMMARY

Background: Ménière's disease or syndrome is characterised 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. This may lead to psychological suffering and a significant reduction in quality of life. Current treatment options include dietary changes, intratympanic injections (through the ear drum) of steroids or antibiotics, positive pressure therapy (for example, the Meniett device), surgery and the drug betahistine (tablets). Betahistine has been used to treat vestibular vertigo in general, but it is thought by some clinicians to be specifically effective for Ménière's disease. The previous version of this Cochrane Review found no evidence of a benefit from the use of betahistine. However, it is still widely being prescribed to patients, especially in Europe. This new review therefore reassesses the effects of betahistine in the treatment of Ménière's disease.

Study characteristics: We found and included 10 randomised controlled trials with a total of 402 adult participants who suffered from Ménière's disease or syndrome. All studies compared the effect of betahistine to placebo. We looked at the effects of betahistine on vertigo symptoms, hearing, aural fullness, tinnitus and disease-specific quality of life. We also looked at adverse (side) effects.

Key results: Although all of the included studies evaluated the effect of betahistine on vertigo, we could not combine their results because of the differences in the participants evaluated and the lack of information about how patients with Ménière's disease were diagnosed, the outcomes measured and the measurement methods used. One study with a low risk of bias found no significant difference between the betahistine group and placebo groups with respect to reduction in vertigo symptoms after a long-term follow-up period (more than three months) (moderate-certainty of evidence). Two studies reported no significant difference in the incidence of the significant adverse effect upper gastrointestinal discomfort (low certainty of evidence). 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 that assessed these outcomes (low- to very low-certainty evidence). Data on aural fullness could not be extracted from any of the studies.

The other adverse effect that was seen on the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effect on the long term included tinnitus, ear discomfort, nervous system disorders, headache, heart burn, skin rash, increased diuresis, extrasystoles

and oral formication. The pooled risk ratio demonstrated a lower risk in favour of placebo over betahistine.

Quality of the evidence: The overall certainty of evidence ranged from moderate to very low, although there was one high-quality study (with low risk of bias). In the remaining studies the risk of bias was generally unclear. In several (older) studies, it remained unclear how patients with Ménière's disease were diagnosed. The results of these studies may therefore not represent patients with Ménière's disease based on the diagnostic criteria that are currently used. The evidence in this review is up-to-date to January 2019.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Vertigo considering together intensity, frequency and duration of symptoms measured by a visual analogue scale (range 0 to 5, questionnaire) Follow-up: up to 3 months	Study population **167 per 1000**	**500 per 1000**	**RR 3.00** (0.97 to 9.30)	36 (1)	⊕⊕○○ LOW [1]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 333 more will have an improvement of vertigo than if they had taken placebo alone.
Vertigo considering together intensity, frequency and duration of symptoms 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 three studies found no significant difference between treatment with betahistine and placebo, including one high quality trial.

Betahistine compared with placebo for Menière's disease or syndrome						
Patient or population: Menière's disease **Setting:** Outpatient clinics **Intervention:** Betahistine **Comparison**: placebo						
Outcomes	**Illustrative comparative risks[*] (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Placebo	**Betahistine**				
Significant adverse (upper gastrointestinal discomfort (yes or no) Follow-up: up to 33 weeks	Study population **86 per 1000**	**83 per 1000**	**RR 0.86** (0.13 to 5.83)	37 (1)	⊕⊕○○ LOW [3]	Non-significant difference between groups. If 1000 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 1000**	**167 per 1000**	**RR 3.0** (0.34 to 26.19)	36 (1)	⊕⊕○○ LOW [1]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 111 more will have an improvement of hearing loss than if they had taken placebo.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
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 1000**	**200 per 1000**	**RR 3.0** (0.15 to 59.89)	10 (1)	⊕○○○ VERY LOW [4]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 200 more will have an improvement of 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 to 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]	Non-significant difference between groups, mean hearing loss score was 9.9 dB higher in the betahistine group.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Tinnitus (improved: yes or no) Follow-up: up to 12 weeks	Study population **167 per 1000**	**444 per 1000**	**RR 2.67** (0.84 to 8.46)	36 (1)	⨁⨁○○ LOW [1]	Non-significant difference. If 1000 patients are treated with betahistine 277 more will have an improvement of tinnitus than if they had taken placebo.
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 **1000 per 1000**	**1000 per 1000**	**RR 1.00** (0.71 to 1.41)	10 (1)	⨁○○○ VERY LOW [4]	Non-significant difference. If 1000 patients are treated with betahistine no difference will be seen in the effect on tinnitus compared to if they had taken placebo.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
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 (-.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 MiniFTF questionnaire.
Other adverse effects (yes or no) Follow-up: up to 3 months	Study population **167 per 1000**	**278 per 1000**	**RR 1.67** (0.47 to 5.96)	36 (1)	⊕⊕○○ LOW [1]	Non-significant difference. If 1000 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 1000**	**165 per 1000**	**RR 2.58** (1.21 to 5.49)	265 (3)	⊕⊕⊕○ MODERATE [5]	Significant difference. If 1000 patients are treated with betahistine, 104 more will have others adverse effects than if they had taken placebo.

Betahistine compared with placebo for Menière's disease or syndrome						
Patient or population: Menière's disease **Setting:** Outpatient clinics **Intervention:** Betahistine **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Placebo	**Betahistine**				
Well-being and disease-specific quality of life based on visual analogue scale (3 point scale with three 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 to 0.40)	144(1)	⊕⊕⊕○ MODERATE [2]	Non-significant difference. The adjusted treatment difference was 0.025 lower in the high dose betahistine group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI; **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** standardized mean difference.

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

1Downgraded one level due to the use of non-validated outcome measures; downgraded one level due to imprecision.
2Downgraded one level due to the use of non-validated outcome measures.
3Downgraded one level due to study limitations (unclear risk of bias for sequence generation, allocation concealment and blinding); downgraded one level due to the level of uncertainty of the diagnosis (use of class II diagnostic criteria).
4Downgraded one level due to study limitations (unclear risk of bias for sequence generation, allocation concealment and blinding); downgraded one level due to the level of uncertainty of the diagnosis (use of class III diagnostic criteria); downgraded one level due to imprecision.
5Downgraded by one level due to inclusion of patients with a level of uncertainty of the diagnosis (use of class II diagnostic criteria)

BACKGROUND

Description of the condition

Menière's disease is characterised 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 two categories: it may be secondary to a number of established inner ear disorders (Menière's syndrome) or idiopathic (Menière's disease). Menière's disease is known to be associated with endolymphatic hydrops, i.e. raised endolymph pressure in the membranous labyrinth of the inner ear [41]. However, hydrops per se does not explain all its clinical features. Nonetheless, both categories may be considered as one 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 [37] which have been revised twice [35,54]. The AAO-HNS 1995 guidelines formulate that a 'definite' diagnosis can be made on the basis of at least two spontaneous episodes of rotational vertigo lasting at least 20 minutes, audiometric confirmation of sensorineural hearing loss, plus tinnitus and/or a perception of aural fullness (**Appendix 1**). More recently diagnostic criteria have also been proposed by the Bárány Society [48].

In a recent study in the USA the prevalence of Menière's disease was estimated at 200 per 100,000 people per year [36]. Menière's disease is most common between 40 and 60 years of age [43]. Vertigo episodes tend to occur in clusters with a period of remission that may last for several months in between the clusters [55]. 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 [51]. In most cases, vertiginous episodes eventually cease completely [58]. The fluctuating, progressive and unpredictable natural history of Menière'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, the loss of hearing; and to alleviate any chronic symptoms (e.g. tinnitus and aural fullness).

Description of the intervention

Betahistine dihydrochloride (betahistine) is an oral drug that has been prescribed to an estimated 130 million people worldwide since its first launch [44]. Although betahistine has been used for vestibular vertigo in general [52], it is thought by some clinicians to be specifically effective for Menière's disease [53]. The recommended daily dose of betahistine

is 24 mg to 48 mg per day divided into two or three single doses containing 8 mg, 16 mg or 24 mg [44]. 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 [52].

How the intervention might work

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 [50]. In addition, inhibition of activity in the vestibular nuclei may contribute to rebalancing neural activity and expedite the recovery process [47, 60]. Studies have shown that betahistine reaches a peak plasma concentration in about one hour and it has a plasma half-life of approximately 3.5 hours. The maximal vestibular therapeutic effect will last approximately three to four hours (EMC 2015). The washout period can be calculated as four times the drug effect [57]. These pharmacological characteristics are thought to reduce the intensity and duration of vertigo symptoms in the short term (under three months) and additionally prevent attacks in the longer term (over three months).

Why it is important to do this review

The previous version of a Cochrane Review found insufficient evidence of a benefit from the use of betahistine [64]. 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 Menière's disease is therefore now warranted.

OBJECTIVES

To assess the effects of betahistine in patients with either Menière's disease or Ménière's syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, including cluster-randomised controlled trials. We excluded quasi-randomised studies. Cross-over trials were eligible if data from before the cross-over were extractable, to avoid the potential for a carry-over phenomenon.

Types of participants

Patients with Menière's disease or syndrome. We classified studies according to the diagnostic criteria used for Menière's disease. We rated studies using the AAO-HNS or the Japanese Society of Equilibrium Research criteria to define probable, definite or certain Menière's disease's 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: any dose regimes or formulations and for any duration of treatment. 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 analysed 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 analysed 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 (three months or under) or long-term (three months or over).

Primary outcomes

Vertigo: the proportion of patients with a reduction in vertigo symptoms (considering the intensity, frequency and duration of those symptoms altogether). Significant adverse effects: upper gastrointestinal discomfort.

Secondary outcomes

Hearing loss: the proportion of patients with progression of hearing loss (more than 15 dB), based on the four-tone average of thresholds at 0.5 kHz, 1 kHz, 2 kHz and 3 kHz, as measured by a pure-tone audiogram. Tinnitus: the proportion of patients with reduction of tinnitus, measured with patient-reported questionnaire scores such the Tinnitus Handicap Index (THI) ([45], see **Appendix 3**), the Tinnitus Functional Index [50], the Tinnitus Handicap Questionnaire [46], the Tinnitus Questionnaire [40], the Tinnitus Reaction Questionnaire [62] and the Tinnitus Severity Scale [59]. Aural fullness: the proportion of patients with reduction of aural fullness, measured by patient-reported questionnaire

scores (e.g. visual analogue scale).Other adverse effects: headache and allergic skin reactions (pruritus, rashes).Well-being and disease-specific health-related quality of life: overall changes as reported particularly on the Functional Level Scale (FLS) (see **Appendix 4**), the Menière's disease Patients Oriented Symptoms Severity Index (MPOSI) and the Dizziness Handicap Inventory (see **Appendix 5**). The FLS will be used as defined by the AAO-HNS 1995 guideline [35]. The questionnaires are validated and often used in trials to assess the change in dizziness-related and Menière's disease-related quality of life [38]. 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 randomised controlled trials 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 to 16 January 2018, re-run on 29 January 2019);Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 16 January 2018, re-run on 29 January 2019);Ovid EMBASE (1974 to 16 January 2018, re-run on 29 January 2019);LILACS (searched 16 January 2018, re-run on 29 January 2019);Web of Knowledge, Web of Science (1945 to 16 January 2018, re-run on 29 January 2019);ClinicalTrials.gov, www.clinicaltrials.gov (searched via the CRS to16 January 2018, re-run on 29 January 2019);World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched 16 January 2018, re-run on 29 January 2019). The Information Specialist modelled 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 randomised controlled trials 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 **Appendix 6.**

Searching other resources

We scanned the reference lists of 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 none-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

Two authors (BE and HZ) 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 (TB, LM, AJ, PB).

Data extraction and management

Two authors (BE and HZ) independently extracted data from the studies using standardised 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 dichotomise these into 'improved' or 'not improved'. If we found studies with more than two groups (e.g. two 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 co-morbidity involved, for example, the presence of migraine and benign paroxysmal positional vertigo (BPPV). For each study, we extracted the following information: study design; duration of study; randomisation; 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);concomitant treatment.

Assessment of risk of bias in included studies

BE and HZ 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 two 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 judgement 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 dichotomised 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 standardised mean difference (SMD). For studies with ordinal data we planned to dichotomise these data wherever possible.

Unit of analysis issues

Cluster-randomised trials

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

Cross-over trials

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

Multi-arm studies

In the event that we found studies with more than two groups (e.g. two or more active treatments being tested against placebo), we established which of the comparisons were relevant to the systematic review. We found only one multi-armed study that used independent groups of participants. As a result, participants were not included in more than one 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 Menière's disease. We regarded bilateral Menière'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 more than one 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 mislabelling 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 [42]. If data were missing we used available case analysis using all data (as reported) for all randomised 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 was 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 Chi2 test. With respect to the I^2 statistic, an approximate guide to interpretation is provided in the Cochrane Handbook for Systematic Reviews of Interventions [42]. If the I2 value was 50% or higher, we considered the data to suffer from substantial or considerable heterogeneity. For the Chi2 test, we used the indicator that if the Chi2 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 less than 0.10. Subsequently, we performed the meta-analysis using fixed-effect (in the absence of heterogeneity) and random-effects modelling (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 analyse treatment differences as a risk ratio (RR), calculated using the Mantel-Haenszel method. Unfortunately, none of the selected studies analysed 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 **Appendix 7**); type of Menière'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 (BE and HZ) 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 four 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 [42] for the following outcomes in the 'Summary of findings' table: 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.

RESULTS

Results of the search

The electronic database search was performed by the Cochrane ENT Information Specialist on 29 January 2019 and identified 1130 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 shown in **Figure 1.**

Included studies

We included 10 randomised controlled trials, the details of which are shown in the Characteristics of included studies table. One of the included studies included more than two treatment arms [1]. Adrion *et al.* was a three-armed study that 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.

Design

In five out of 10 studies a prospective, cross-over comparison design was used [2,3,4,5,10]. In two of these five studies data prior to crossover were extractable. In the remaining five studies a parallel group design was used. All studies were described as being double blinded.

Sample sizes

The sample size ranged from 10 [8] to 221 [1]. A total of 402 patients had results reported across the 10 included studies. No additional results from unpublished studies were included in this review.

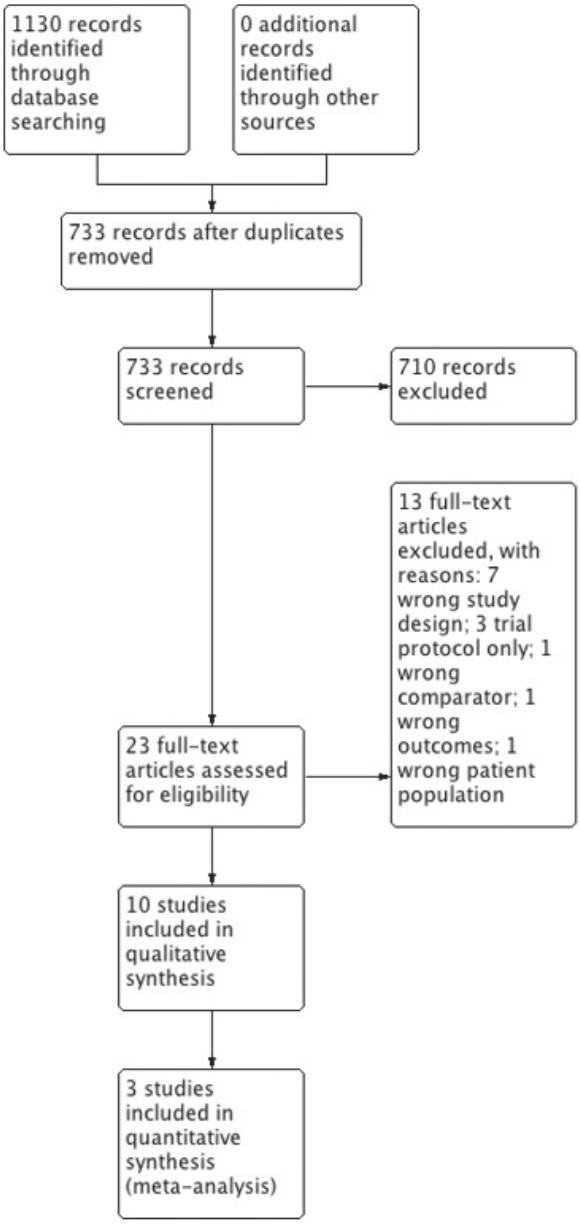

Figure 1. Process for sifting search results and selecting studies for inclusion

Setting

All studies were conducted in otorhinolaryngology departments within hospitals. The majority of the studies were single-centred. Adrion *et al.* and Mira *et al.* were multicentre studies [1,6]. The selected studies took place in Germany [1,5], the UK [2,4], the USA [3], Italy [6,8,9], Japan [7] and the Netherlands [10].

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. Adrion *et al.* applied the internationally recognised criteria for 'definite' Ménière's disease and was therefore classified as class 'I' (see Types of participants) [1]. Both Mira *et al.* and Schmidt *et al.* 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' [6,10]. We classified Burkin *et al.*, Elia *et al.*, Frew *et al.*, Meyer *et al.*, Okamato *et al.*, Ricci *et al.* and Salami *et al.* as class 'III' since no specific predefined diagnostic criteria were provided or details of how vertigo attacks, hearing loss and tinnitus were evaluated [2-5,7-9].

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 [2,3], 24 mg [9], 2 mg [4,6], 36 mg [5,7](two times daily with three pills), 72 mg [10] and 144 mg [8]. One study compared high-dose betahistine (144 mg per day, in three doses) and low-dose betahistine (48 mg per day, in two doses) to placebo [1]. Schmidt *et al.* used a slow release formulation [10]. Assessment with regards to compliance was only reported in detail by Adrion *et al.*[1]. 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 (less than three months), except for Adrion *et al.*, Mira *et al.* and Schmidt *et al.* [1,6,10]. Adrion *et al.* evaluated the effects of all three interventions arms after nine months, whereas Schmidt *et al.* defined a follow-up period of eight months [1,10]. Mira *et al.* assessed the effects after three months [6]. All included studies used one of our pre-specified outcome measures (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 three studies the frequency of attacks was used as the main outcome to measure the effect of betahistine after a long-term follow-up (three 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 [1,6,10]. Burkin *et al.* quantified whether patients experienced dizziness or not, while Elia *et al.* based the effect of treatment on a subjective scale, which ranged from 0 to 3 [2,3]. The remaining studies used different ordinal scales to quantify the severity/intensity of the vertigo attacks by means of four-point scale [4], a five-point scale [5], a three-point scale [7], and a vertigo maximum intensity of the episode and the mean duration of each vertigo episode [9]. Ricci *et al.* used the AAOO classification in which both the effect on vertigo and hearing were combined and classified into four groups (A to D) [8].

Significant adverse effects: upper gastrointestinal discomfort

The incidence of upper gastrointestinal discomfort was reported by two studies [6,10], which both assessed the effect of betahistine in the long term (three months or more).

Hearing loss

The effect of betahistine on hearing loss was assessed in seven studies in variable ways. Adrion *et al.* reported results of pure tone audiometry per frequency (250 Hz, 500 Hz, 1000 Hz and 2000 Hz) and reported the adjusted mean change for placebo; these were compared with the adjusted mean difference for the low dose and high-dose betahistine [1]. Frew *et al.* reported the amount of deafness by means of a four-point scale without any further details [4]. Meyer *et al.* reported the mean frequency scores with standard deviation based on the three-point threshold of 0.5 Hz, 1.0 Hz and 2.0 kHz [5]. Okamato *et al.* used a three-point scale by which subjective changes in hearing were assessed [7]. The mean threshold for the frequencies of 0.5 Hz, 1.0 Hz and 2.0 Hz were classified by the ANSI in the study of Ricci *et al.* resulting in six classes (0 to 25 dB = normal, 26 to 40 dB = mild hearing loss, 41 to 55 dB = moderate hearing loss, 56 to 70 dB = moderately serious hearing loss; 71 to 90 dB = serious hearing loss; 91 dB = very serious hearing loss) [8]. Salami *et al.* used the mean threshold at frequencies of 0.25 kHz, 0.5 kHz, 1.0 kHz and 2.0 kHz but no mean and standard deviations were reported [9]. Schmidt *et al.* used the mean threshold scores based on the frequencies from 0.25 kHz to 2 kHz [10].

Tinnitus

All but one study reported changes in tinnitus symptoms before and after treatment [2]. Adrion *et al.* used the MiniTF questionnaire, where as Elia *et al.* used a subjective scale that ranged from 0 to 3 (3 = incapacitating, 2 = severe, 1 = moderate, 0 = not present) [1,3]. Frew *et al.* used a four-point scale, Meyer *et al.* a five-point scale and Okamato *et al.* a three-point scale [4,5,7]. Mira *et al.* reported tinnitus as part of the 'associated symptoms' which all together were scored with aural fullness, nausea and vomiting by means of four-point scale (0 = absent, 1 = mild, 2 = severe, 3 =disabling) [6]. Both Ricci *et al.* and Salami *et al.* used a scale ranging from 0 to 6, whereas Schmidt *et al.* used a four-point scale and the minimum masking level in dB with mean and standard deviations to assess the effect on tinnitus [8,9,10].

Aural fullness

Aural fullness was reported by seven of the selected studies, except for Burkin *et al.* and Okamato *et al.* [2,7] Adrion *et al.* reported that participants were instructed to record co-existing symptoms such as aural fullness but data were not shown in the results section [1]. In line with previous outcomes Frew *et al.* used a four-point scale and Meyer *et al.* a five-point scale [4,5]. In line with the tinnitus outcome Mira *et al.* reported aural fullness as part of the 'associated symptoms' questionnaire [6]. Both Ricci *et al.* and Salami *et al.* again used a scale ranging from 0 to 6 [8,9]. Aural fullness was evaluated in Schmidt *et al.* 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 four studies [1,6,7,10]

Well-being and disease-specific health-related quality of life

The effect on well-being was evaluated in two studies [1,6]. Adrion *et al.* used the Dizziness Handicap Inventory (DHI) whereas Mira *et al.* 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 table).

Risk of bias in included studies

Two authors (BE and HZ) 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 reported clearly. This can be seen in the number of unclear scores regarding these matters (see Figure 2). All studies were reported to be double blinded whereas only Adrion *et al.* and Okamato *et al.* reported in detail how blinding was accomplished [1,7]. 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 summarised in **Figure 2** and **Figure 3**.

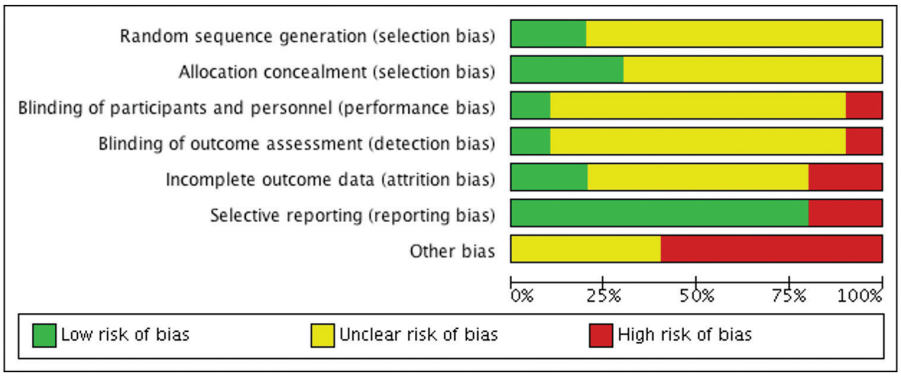

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Sequence generation

We considered the risk of selection bias due to inadequate method description on sequence generation to be unclear in seven studies [2,3,4,5,6,9,10] and low in the remaining three studies [1,7,8]. In the study performed by Adrion *et al.* a 1:1:1 ratio was used creating a high dose betahistine, low dose betahistine and placebo group [1]. Okamato *et al.* used a table of random numbers created by a third party independent from the medical institution [7]. Likewise, Ricci *et al.* assigned patients to the betahistine or placebo group based on a random list [8].

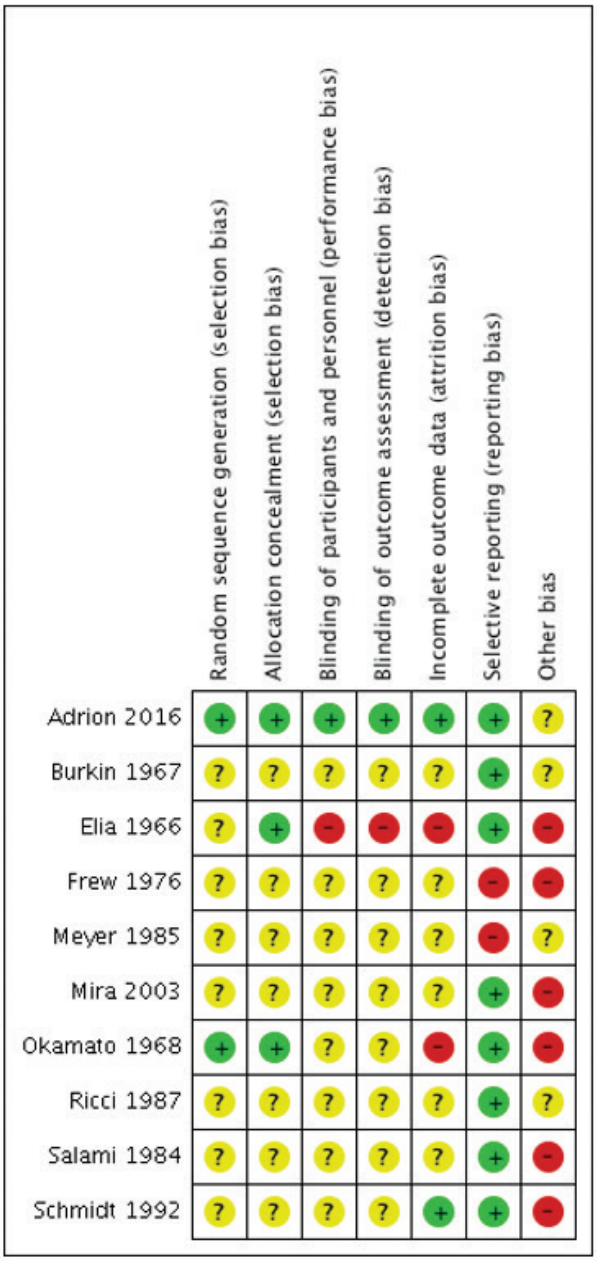

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation concealment

The allocation concealment was rated as unclear in all but three studies [1,3,7]. Elia *et al.* defined that a fifth person who was not involved in the study coded the tablets [3]. 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.* described in detail that allocation concealment was performed by means of an Internet-based randomisation schedule which was generated by an investigator with no clinical involvement in the trial [1]. The patients, clinicians, core laboratories, and trial staff were all described as blinded to treatment allocation. Finally, Okamato *et al.* 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 [7].

Baseline characteristics

In two studies [3,4] no details on baseline characteristics were reported. Both studies were rated as "class III" with regards to the diagnostic criteria applied to include patients as Menière's disease. Although Okamato *et al.* described the sex distribution among the population, no information on age was given and unclear diagnostic criteria were used to describe the studies population (class III) [7]. With regards to the robustness of diagnostic criteria used to include patients with Ménière's disease, seven studies were rated as " class III" [2,3,4,5,7,8,9] two as "class II" [6,10] and one [1] as "class I". No significant differences were found in the studies that presented baseline characteristics for age and sex distribution [1,6, 8,9,10]. Only Adrion *et al.,* Ricci *et al.*; Salami *et al.* and Schmidt *et al.* reported the duration of disease before the start of the trial [1,8,9,10]. The effect of betahistine on hearing loss was objectively assessed by Adrion *et al.*, Ricci *et al.*; Salami *et al.* and Schmidt *et al.*, although specific hearing score outcomes were only given by Adrion *et al.* and Schmidt *et al.*.

Blinding

Due to inadequate blinding in seven out of the nine studies [2-6, 8-10], there was a risk of performance bias and detection bias in most studies. Although Elia *et al.* described that a fifth person coded the tablets given during trial execution the same sequence was repeated (A, B, C and D) was used in all patients [3]. As a result, the intervention could be predicted by the patients, physician or the statistician and was therefore considered to be of high risk. Ricci *et al.* described that a random list was used to divide participants but no information on blinding was provided in the methods section [8]. Therefore, we considered that there was still a considerable risk of inadequate blinding in both studies.

Incomplete outcome data

We considered only two studies to have a low risk of attrition bias [1,10] as concrete reasons of non-completion of the trial were given. In the studies performed by Burkin *et al.*, Frew *et al.*, Ricci *et al.* and Salami *et al.* there was no mentioning of dropping out or discontinuation of trial participation for any reason [2,4,8,9]. But as it remained unclear how many patients were analysed 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 *et al.*, Meyer *et al.*; Mira *et al.* and Okamato *et al.* [3,5,6,7]. In the study performed by Elia *et al.*, four of 20 participants dropped out due to non-compliance to the trial and migration of participants [3]. In two patients, it remained unclear whether they had received betahistine or placebo. Meyer *et al.* 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 [5]. The participants studied by Mira *et al.* were not balanced across groups, for which they did not correct in the analyses. Last, Okamato *et al.* reported that four patients out of 36 dropped out (11%), not due to adverse effects of the drug use, but any other reason for drop-out was not clarified [7].

Selective reporting

A study protocol was available for the study performed by Adrion *et al.*, published prior to the execution of the study, from which we found that predefined outcomes were evaluated in the published version of the final manuscript, reporting on study results [1]. In seven 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 [2,3,6,7,8,9,10]. The studies performed by Frew *et al.* and Meyer *et al.* 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 [4,5].

Other potential sources of bias

None of the studies had a low risk bias on other potential sources of bias. Adrion *et al.* did not reveal data on pre-randomisation attack frequency although it was considered as an inclusion criterion [1]. 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 Burkin *et al.*, Elia *et al.*, Meyer *et al.*, Ricci *et al.* and Salami *et al.* reported no details on how statistical analysis was performed, the authors concluded that a positive effect was found of betahistine on symptoms of Menière's disease, this was considered to be a high potential source of bias [2,3,5,8,9]. Frew *et al.* used one-sided testing which should have been two-sided [4].

Moreover, standard deviations were not reported and we considered a high risk of selection bias due to a pre-treatment period, in which the investigator was allowed to exclude placebo responders hereby decreasing external validity of the study results. Sample size calculation performed by Mira *et al.* was done without referring to previous studies performed [6]. In the outcome section, improvement of associated symptoms including tinnitus, fullness of the ear, nausea and vomiting which were summarised in one figure. However, it was unclear how performed and whether data were complete. The trial medication during the execution of the trial by Okamato *et al.* was supplied by Eisai Co, the role of this subsidising party remained unclear [7]. We considered there was a high risk of bias in the study by Schmidt 1992 since the intention to treat analysis was not correctly executed because one patient crossed over due to side effects earlier than the protocol stated. Furthermore, the data were analysed per protocol [10]. Moreover, in these analyses the authors did not account for the loss of follow-up from drop-outs.

Effects of interventions

See: **Summary of findings table 1**.

Betahistine versus placebo

Primary outcomes

Proportion of patients with 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 four cross-over studies [2-5]. Ricci *et al.* combined the effect on vertigo and hearing loss in one outcome and no numerical data were presented [8]. No data could be extracted from Salami *et al.* [9].

Short-term follow-up (less than three months)

Okamato *et al.* used a three-point visual analogue scale from which the proportion of patients with an improvement of vertigo symptoms at short-term follow-up was quantified. The risk ratio (RR) was 3.0 (95% confidence interval (CI) 0.97 to 9.30) in favour of betahistine (GRADE: low certainty) (**Analysis 1.1**) [7].

Long-term follow-up (more than three months)

Adrion *et al.*, Mira *et al.* and Schmidt *et al.* all assessed the effect of betahistine after a long-term follow-up [1,6,10]. Data could not be pooled because there was significant heterogeneity in outcomes between studies (**Analysis 1.2**) and no raw data to impute

standard deviations were available. Mira *et al.* described a significant improvement in the monthly vertigo attack frequency without presenting absolute baseline and endpoint data for the placebo group [6]. Schmidt *et al.* found no difference between the betahistine and placebo group in the effect on imbalance scores [10]. Adrion *et al.* was the study with the lowest risk of bias; this study found no favourable effect after comparing high-dose and low dose betahistine to placebo [1]. In summary, two studies found no favourable effect for betahistine which included one study with a high quality [1,10]. We assessed the certainty of the evidence for this outcome as moderate (GRADE).

Significant adverse effect: upper gastrointestinal discomfort

Both Mira *et al.* and Schmidt *et al.* reported no significant difference in the incidence of upper gastrointestinal discomfort. The pooled risk ratio was 0.86 (95% CI 0.13 to 5.83; 2 studies; 118 participants) in favour of placebo (**Analysis 1.3**) (GRADE: low certainty) [6,10].

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) [7,8] and continuous data based on means with corresponding four-point thresholds for the frequencies from 0.25 kHz to 2.0 kHz [10]. Data from the four remaining studies could not be pooled because only data per frequency were reported and no mean four-point threshold score could be calculated [1], no pre-cross over data were available [4,5], or no data were presented [9]. No significant difference between the betahistine and placebo group could be found in the included studies.

Short-term follow-up (less than three months)

In the short term, Okamato *et al.* reported a risk ratio of 3.00 (95% CI 0.34 to 26.19; 1 study; 36 participants) for the improvement of hearing (GRADE: low certainty) (**Analysis 1.4**) [7].

Long-term follow-up (more than three months)

The long-term effect on hearing loss was evaluated by Ricci *et al.*, which reported a risk ratio of 3.00 (95% CI 0.15 to 59.89; 1 study; 10 participants) (GRADE: very low certainty) (**Analysis 1.5**) [8]. Schmidt *et al.* found no difference between the betahistine group and the placebo group based on mean threshold scores at long-term follow-up (mean difference (MD) 10.10, 95% CI -0.97 to 21.17; 1 study; 35 participants) (GRADE: low certainty) (**Analysis 1.6**) [10].

Tinnitus

Short-term follow-up (less than three months)

The effect of betahistine on tinnitus was evaluated at short-term follow-up by Okamato *et al.*, which reported the proportion of participants with an improvement as a risk ratio of 2.67 (95% CI 0.84 to 8.46; 1 study; 36 participants) (GRADE: low certainty) (**Analysis 1.7**). These results are not statistically significant or clinically relevant [7].

Long-term follow-up (more than three months)

At long-term follow-up, Ricci *et al.* found no difference between the betahistine group and the placebo group based on the proportion of patients without deterioration of hearing (risk ratio 1.00, 95% CI 0.71 to 1.41; 1 study; 10 participants) (GRADE: very low certainty) (**Analysis 1.8**) [8]. Long-term effect was reported as the standardised mean difference based on the MiniTF in Adrion *et al.*, which found no difference in the difference between betahistine and placebo (SMD -0.16, 95% CI -0.48 to 0.17; 1 study; 144 participants) (GRADE: moderate certainty)(**Analysis 1.9**) [1].

Aural fullness

Data on aural fullness could not be extracted from any of the seven studies because first period, pre- cross-over data could not be extracted [4,5], no aural fullness data were presented [1], no numerical data were presented [9,10], data for the betahistine group and placebo group were not shown [8] or results were reported only with a P value without data on baseline absolute values and endpoint values [6].

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 (less than three months)

Okamato *et al.* found no significant difference in other adverse effects between the betahistine and placebo group (RR 1.67, 95% CI 0.47 to 5.96; 1 study; 36 participants) (GRADE: low certainty) (**Analysis 1.10**) [7].

Long-term follow-up (more than three months)

At long-term follow-up, Adrion *et al.*, Mira *et al.* and Schmidt *et al.* found a lower risk ratio in favour of placebo when compared to betahistine [1,6,10]. The pooled risk ratio was 2.58 (95% CI 1.21 to 5.49; 3 studies; 265 participants) (GRADE: moderate certainty) (**Analysis 1.11**).

Well-being and disease-specific health-related quality of life

Disease-specific health-related quality of life was evaluated by Mira *et al.*, 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 [6]. Adrion *et al.*evaluated disease-specific health-related quality of life by means of the Dizziness Handicap Inventory (DHI) which were reported as standardized mean differences compared to placebo [1]. 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 (**Analysis 1.12**).

DISCUSSION

Summary of main results

The current review includes 10 randomised controlled trials (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 of 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 [1]. 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 two studies that reported this outcome [6,10]. 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 one study based a non-validated visual analogue scale which lacked information whether or not results were statistically better in the betahistine compared to the placebo group. The other adverse effect that was seen on the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effect on the long term included tinnitus, ear discomfort, nervous system disorders, headache, heartburn, skin rash, increased diuresis, extrasystoles and oral formication. The pooled risk ratio demonstrated a lower risk in favour of placebo over betahistine. 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 [1].

Overall completeness and applicability of evidence

Specific diagnostic criteria were used to select patients for trial participation in only one of the included studies [1]. 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 six 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 to 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 one high-quality study was included [1]. 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 standardised and comparable methods to assess the effect on vertigo in order to increases 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), 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 randomisation, allocation concealment, blinding of personnel, participants and outcome assessors were performed. Only one of the included studies had a pre-published 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 minimise 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 summarising of data or make pooling of data more feasible.

Agreements and disagreements with other studies or reviews

At least two other reviews have evaluated the effect of betahistine in the treatment of Ménière's disease [47,53]. Both reviews concluded that there is a favourable effect of betahistine on vertigo. Lacour *et al.* is an expert opinion paper, which describes the definition of Ménière's disease, its epidemiology, pathophysiology and the role for betahistine in its therapeutic management including the mechanisms of action that are hypothesised to play a role in the potential positive effect of the drug [47]. The favourable clinical effect of betahistine is evaluated by means of a narrative summary of the results found in the Mira *et al.* study [6]. 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 Menière's disease and related conditions. Nauta *et al.* 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 odd ratio (OR) was 2.58 (95% confidence interval (CI) 1.67 to 3.99). When restricted sub-analyses of Ménière's disease patients only were performed the average OR was 3.37 (95% CI 2.14 to 5.29). No analysis of validity or risk of bias assessment was presented. Cochrane ENT has published two systematic review 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 (1025 participants) [52]. Out of these 17 studies, five evaluated the effect of betahistine for Ménière's disease from which the pooled risk ratio was 1.56 (95% CI 0.92 to 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 standard diagnostic criteria. Moreover, the incidence of adverse effects was similar for both betahistine and placebo. The second review evaluated the effect of betahistine on tinnitus and included five studies (303 to 305 participants) [61]. This review concluded that there is no evidence to suggest that betahistine has an effect on subjective idiopathic tinnitus. In summary, previous reviews have either concluded 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 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.

AUTHORS CONCLUSIOSN

Implications for practice

High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, one 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 [1]. Betahistine appears to be generally well tolerated and the risk of gastro-intestinal 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, non-invasive 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 three 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 randomisation and blinding needs to be low to avoid any placebo effect. Standardised diagnostic criteria should be rigorously applied. A standardised method of designing and reporting trial results such as the CONSORT statement should be used (CONSORT 2010). We recommend validated, patient-centred 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 standardised 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 one high-quality study [1], 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, as well as the huge effort involved in conducting a trial on the part of patients, doctors and researchers, as well as 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 prioritised

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CHARACTERISTICS OF INCLUDED STUDIES

Adrion 2016

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 221 participants were allocated to either betahistine high dose, low dose or placebo for a nine 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, 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), high dose betahistine 56.1 (SD 12.6)Gender: male (%) for placebo 35 (47), low dose betahistine 39 (53), high dose betahistine 35(47), total 109 (49). **Included criteria**: Patients aged 18-80 years were eligible for enrolment if they presented with two or more definitive spontaneous episodes of vertigo of at least 20 minutes' duration, had audiometrically documented hearing loss on at least one occasion, and tinnitus or aural full-ness in the treated ear, excluding other possible causes of vertigo. These factors made up a diagnosis of definite unilateral or bilateral Meniere's disease, fulfilling the criteria of the 1995 American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) guideline. Furthermore, patients had to be in an active phase of the disease, with at least two vertigo attacks per month in at least three consecutive months before enrolment. Female patients of childbearing potential were only included if they had a negative serum pregnancy test within seven days before initiation of treatment and were willing to practice acceptable methods of birth control during treatment and for three months after treatment; CLASS I. **Excluded criteria**: Exclusion criteria were diagnosis of other central or peripheral vestibular disorders such as vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, as well as phobic postural vertigo. Patients were excluded if they had known contra-indications or sensitivity to betahistine, such as bronchial asthma, pheochromocytoma, treatment with other antihistaminic drugs, ulcer of the stomach or duodenum, or severe dysfunction of liver or kidney. Safety-related exclusion criteria were severe coronary heart disease or heart failure, persistent uncontrolled hypertension with systolic blood pressure higher than 180 mm Hg or diastolic blood pressure higher than 110 mm Hg, life expectancy less than 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. **Pre-treatment:** Not reported.

Interventions	**Intervention group:** **Low dose betahistine: 2**4 mg per capsule, 6 capsules three 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:** three 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 capsules with an identically appearing filled with mannitol and Aerosil but not containing any active ingredient was administered as placebo three 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 day 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 analysed, similar to tinnitus with the adjusted mean change comparing placebo to low and high dose of betahistine
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 centres (14) Comments: None Authors name: Christine Adrion Institution: German centre 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 judgement**	**Support for judgement**
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 randomisation schedule stratified by study site, fixed block size was three 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, trial staff were blind to treatment allocation
Blinding of outcome assessment (detection bias)	Low risk	Patients, clinicians, core laboratories, trial staff were blind to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Reasons for drop-outs were given for all participants.
Selective reporting (reporting bias)	Low risk	All predefined outcomes were analysed
Other bias	Unclear risk	Pre-randomisation attack frequency was not documented although considered as an inclusion criterion. Data was not shown with respect to duration and age at the onset of disease but groups were well balanced based on these characteristics.

Burkin 1967

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 22 participants were allocated to either betahistine or placebo for two weeks and then switch to placebo or betahistine, four 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 **Included criteria:** Diagnosed as having Meniere's syndrome, careful examination of each patient and a thorough evaluation of their symptoms; CLASS III **Excluded criteria:** None predefined **Pre-treatment:** 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 Authors 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 judgement**	**Support for judgement**
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 randomisation 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 outcome 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.

Elia 1966

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 20 participants were allocated to either betahistine (A or C) or placebo (B or D) for two weeks and then switch to placebo or betahistine. This was repeated for two more times. **Number completed:** 16 participants, unclear whether this was equally balanced across both groups **Participants baseline characteristics:** **Age:** not reported **ender:** not reported **Included criteria:** Suffering from intractable vertigo for at least four months. Readily available for examination. Would agree to continue therapy for 8 weeks. Examination every 14 days; CLASS III **Excluded criteria:** None predefined **Pre-treatment:** 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 Authors 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 judgement**	**Support for judgement**
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, B, C and D) was used in all patients, could be predicted by the patients, physician and the statistician.
Blinding of outcome assessment (detection bias)	High risk	The same sequence was repeated (A, B, C and D) was used in all patients, 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 non-compliance to the trial and change of location of the participants.
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcome 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 Menière's disease.

Frew 1976

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 26 participants were allocated to either betahistine or placebo for eight weeks and then switch to placebo or betahistine. This was repeated for two 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 **Included criteria:** diagnosis was based on paroxysmal attacks of rotational vertigo, tinnitus and fluctuating sensorineural deafness; CLASS III **Excluded criteria:** none predefined **Pre-treatment:** 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 was given
Declaration of interest	None declared
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
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 six patients withdrew, described as "unable to co-operate", no reasons for drop-out 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 summarised by the investigator.
Other bias	High risk	One-sided testing which should be two-sided, standard deviation not reported; high risk of selection bias due to pre-treatment period, allowing the investigator to exclude placebo responders (decreases external validity of study results).

Meyer 1985

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 40 participants were allocated to either betahistine or placebo for six weeks and then switch to placebo or betahistine. **Number completed:** 40 participants **Participants baseline characteristics:** **Age:** 24-67 years **Gender:** 21 (56) **Included criteria:** Based on patient history, audiometric hearing test results, vestibular testing, radiologic results, neurological and orthopaedic research; CLASS III **Excluded criteria:** Allergic reactions, gastritis, gastric ulcus, hypertonic, liver dysfunction (contra-indication for use of betahistine) **Pre-treatment:** One year before study treatment, during treatment (at 2, 6, 12 weeks) and after one 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 two 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 three-tone average of thresholds at 0.5 kHz, 1 kHz, 2 kHz
Identification	Sponsorship source: Unknown Country: Germany Setting: HNO-Klinik und Poliklinik Bereich Medizin der Humboldt-Universiat at Berlin Comments: No comment Authors 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 judgement**	**Support for judgement**
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 participant 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 test although it remains unclear which diagnostic criteria were mandatory to full fill the diagnosis of Meniere's disease, unclear which statistical analysis were used for each outcome.

Mira 2003

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Sample size:** **Number randomised:** 41 participants were allocated to betahistine, 40 participants were allocated to placebo for 3 months **Number completed:** 81 participants **Participants baseline characteristics:** **Age:** not reported **Gender:** not reported **Included criteria:** Probable or possible MD based on the AAO HNS criteria, Out or in-patient, between 18-65 years old, 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 **Excluded 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, 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. **Pre-treatment:** 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), data was 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 from Grunethal-Formenti, Milan Italy **Country:** Italy **Setting:** Multicentre **Comments:** No comment **Authors 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 judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear who made and kept the randomisation 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
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 summarised in one figure whereas it remains unknown how calculations were performed, unknown if complete data was available

Okamato 1968

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 40 participants were allocated to betahistine or placebo **Number completed:** 36 participants, 2 drop outs in the betahistine and 2 drop outs placebo group **Participants baseline characteristics:** **Age:** not reported **Gender:** 13 males (36%) **Included criteria:** diagnosed as Meniere'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 **Excluded criteria:** not defined **Pre-treatment:** not reported
Interventions	**Intervention group:** betahistine dihydrochloride, 36 mg per day, 6 tablets per day, 2 times 3 tablets daily for two weeks **Comparator group:** 6 tablets per day. 2 times 3 tablets daily prepared identically in appearance, taste and smell for two 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:** **Authors 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 subsidising party was

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
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 drop outs 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 subsidising party was

Ricci 1987

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 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%) **Included criteria:** Meniere's disease patients; CLASS III **Excluded criteria:** Hypertensivity against betahistine, peptic ulcer, gastroduodenitis, pheochromocytoma, asthma, grave asthenia, arterial hypertension, renal or hepatic insufficiency **Pre-treatment:** 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 using of anti-vertigo drugs, drugs acting on the cerebral circulation, anti-histamines and histamines mimetics were 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 kHz, 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:** **Authors 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 judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assigned to the treatment groups based on a randomisation 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 drop outs or lost to follow-up was reported
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcome 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

Salami 1984

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 15 participants were allocated to betahistine, 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%) **Included criteria:** Vascular of neurovascular Meniere's syndrome, criteria for diagnosis were not stated; CLASS III **Excluded criteria:** Patients with vertigo of extra-vestibular origin (visual, proprioceptive mental), patients with a history of peptic ulcer, pheochromocytoma, asthma, ictus cerebri (cerebral shock, exhaustion (grave asthenia)), arterial hypertension, patients with hepatic or renal insufficiency, patients with alteration of gonad or thyroid function, those exposed to prolonged treatments with drugs that are potentially ototoxic (quinine, salicylates, aminoglycoside, furosemide) those regularly using narcotics, lactating or pregnant women, and those with a proven hypersensitivity to betahistine hydrochloride. **Pre-treatment:** 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 using of anti-vertigo drugs, drugs acting on the cerebral circulation, anti-histamines and histamines mimetics were 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 kHz, 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:** Outpatient department Otorhinolaryngology **Comments:** **Authors 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 judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on random sequence generation was 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 participant and personnel was available
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 drop outs 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 outcome 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 were performed

Schmidt 1992

Methods	**Study design:** randomised controlled trial **Study grouping:** crossover
Participants	**Sample size:** **Number randomised:** 40 participants were allocated to either to betahistine or placebo who switch from therapy after a period of 16 weeks, outcomes were measured every month with a total follow-up period 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%) **Included criteria:** Complete MD, unilateral or bilateral, according to the Utrecht working definition, i.e.: 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 **Excluded 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, it 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 tumour, recent head trauma, Parkinson's disease, epilepsy, multiple sclerosis or any other generalised disease, operated upon because of MD, using antihistamines, anti-vertiginous 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 three months, who had experienced side effect during previous use of betahistine dihydrochloride **Pre-treatment:** One week with no use of any medication to create a wash-out effect.
Interventions	**Intervention group:** betahistine dihydrochloride 24 mg 3 times per day, total 72 mg per day with a sustained formula **Comparator group:** placebo capsules with an identical appearing 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 to 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, 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:** **Authors 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	

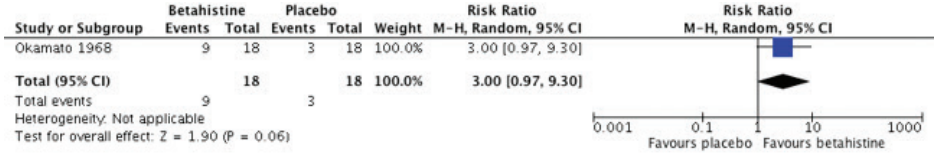
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generations (selection bias)	Unclear risk	No details on random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available.
Blinding of participants 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 drop outs 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 not applied because one patient crossed over due to side effects earlier than the protocol described but the data were analysed per protocol. Follow-up data from drop outs was not accounted for.

Data and analyses

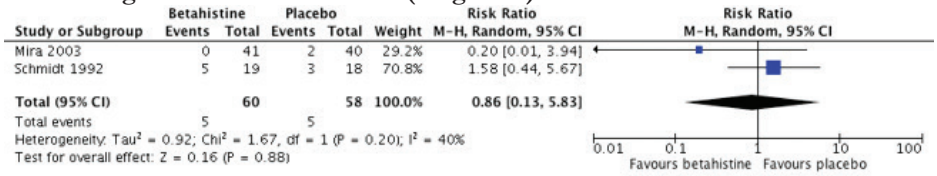
1 Betahistine versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Vertigo considering together intensity, frequency and duration of symptoms (short-term)	1	36	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.97, 9.30]
1.2 Vertigo considering together intensity, frequency and duration of symptoms (long term)	3	259	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Significant adverse effects (long term)	2	118	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.13,5.83]
1.4 Hearing loss (short term)	1	36	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.34, 26.19]
1.5 Hearing loss (long term)	1	10	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.15, 59.89]
1.6 Hearing loss (long term)	1	35	Mean Difference (IV, Random, 95% CI)	10.10 [-0.97, 21.17]
1.7 Tinnitus (short term)	1	36	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.84, 8.46]
1.8 Tinnitus (long term)	1	10	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.41]
1.9 Tinnitus (long term)	1	144	Std. Mean Difference (IV, Random, 95% CI)	-016 [-0.48, 0.17]
1.10 Other adverse effects (long term)	1	36	Std. Mean Difference (IV, Random, 95% CI)	1.67 [0.47, 5.96]
1.11 Other adverse effects (long term)	3	265	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.21, 5.49]
1.12 Well-being and disease-specific quality of life (long term)	1	144	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.25, 0.40]

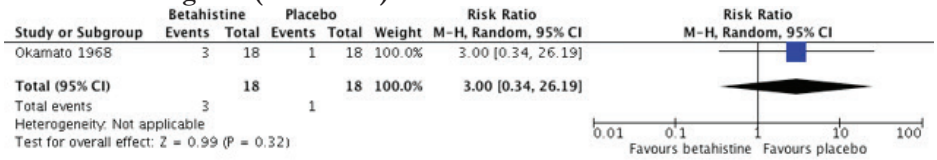
1.1 Vertigo considering together intensity, frequency and duration of symptoms (short-term)



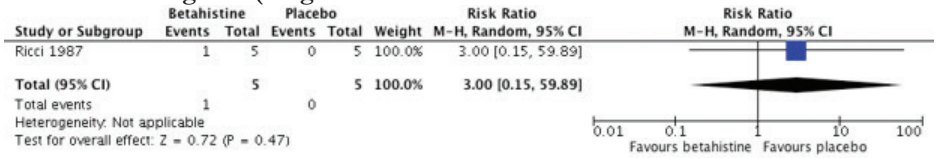
1.3 Significant adverse effects (long term)



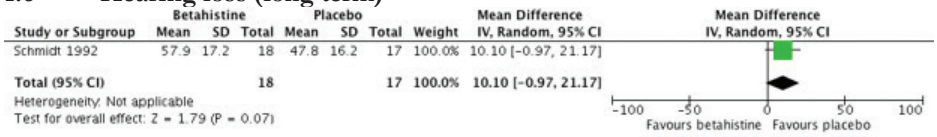
1.4 Hearing loss (short term)



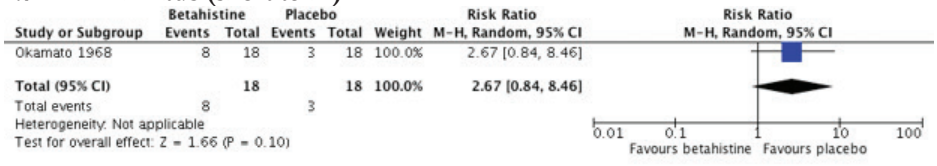
1.5 Hearing loss (long term



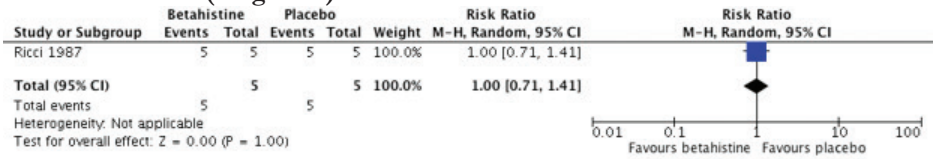
1.6 Hearing loss (long term)



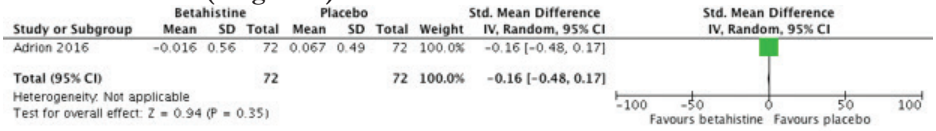
1.7 Tinnitus (short term)



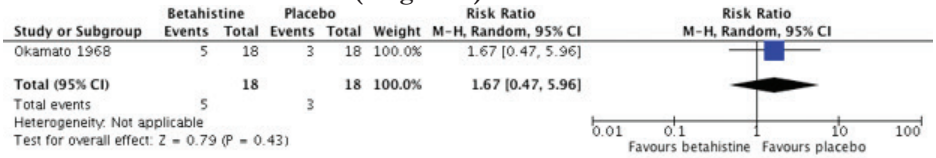
1.8 Tinnitus (long term)



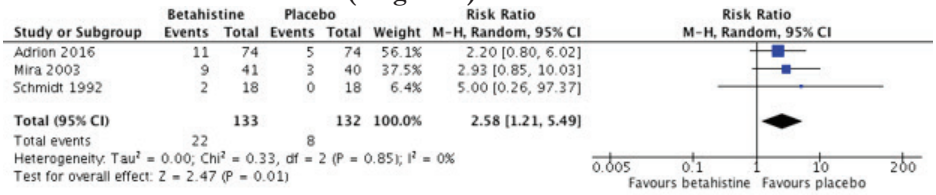
1.9 Tinnitus (long term)



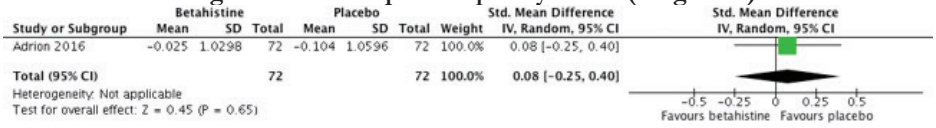
1.10 Other adverse effects (long term)



1.11 Other adverse effects (long term)



1.12 Well-being and disease-specific quality of life (long term)



APPENDICES

Appendix 1. Diagnostic criteria defined for Menière's disease by the American Academy of Otolaryngology – Head and Neck Surgery in 1995

TABLE I

AAO-HNS 1995 CRITERIA FOR MÉNIÈRE'S DISEASE

Certain Ménière's disease
– Definitive Ménière's disease
– Histopathological confirmation
Definite Ménière's disease
– ≥2 definitive spontaneous vertigo episodes of 20+ mins duration
– Audiometrically documented hearing loss on 1 occasion
– Tinnitus or aural fullness in treated ear
– Other causes excluded
Probable Ménière's disease
– 1 definitive spontaneous vertigo episode of 20+ mins duration
– Audiometrically documented hearing loss on 1 occasion
– Tinnitus or aural fullness in treated ear
– Other causes excluded
Possible Ménière's disease
– Episodic vertigo of Ménière's disease type, without hearing loss, or,
– Fluctuating or fixed SNHL, with disequilibrium but with no definitive episodes
– Other causes excluded

AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery; mins = minutes; SNHL = sensorineural hearing loss

Appendix 2. AAO-HNS outcome measures

The AAO-HNS Committee on Hearing and Equilibrium proposed the "control of vertigo" as a main objective outcome measure when assessing therapy in Ménière's disease. The number of attacks six months prior to treatment is compared to the number of attacks in the period between 18 and 24 months following treatment. The resulting number indicates the extent of "control of vertigo". The AAO-HNS further divides the control of vertigo into classes, where Class A (CoV = 100% control) is complete control and class B (CoV 99 to 60%%) is substantial control. They recommend a period of at least two years of follow-up in order to assess fully the effect of the intervention. We will also consider studies with shorter periods of follow-up for this review (AAO-HNS 1995).

Appendix 3. Tinnitus Handicap Inventory

The purpose of this questionnaire is to identify difficulties that you may be experiencing because of your tinnitus. Please answer every question. Please do not skip any questions.

1. Because of your tinnitus, is it difficult for you to concentrate?	Yes	Sometimes	No
2. Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	Sometimes	No
3. Does your tinnitus make you angry?	Yes	Sometimes	No
4. Does your tinnitus make you feel confused?	Yes	Sometimes	No
5. Because of your tinnitus, do you feel desperate?	Yes	Sometimes	No
6. Do you complain a great deal about your tinnitus?	Yes	Sometimes	No
7. Because of your tinnitus, do you have trouble falling to sleep at night?	Yes	Sometimes	No
Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?	Yes	Sometimes	No
10. Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
10. Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
11. Because of your tinnitus, do you feel that you have a terrible disease?	Yes	Sometimes	No
12. Does your tinnitus make it difficult for you to enjoy life?	Yes	Sometimes	No
13. Does your tinnitus interfere with your job or household responsibilities?	Yes	Sometimes	No
14. Because of your tinnitus, do you find that you are often irritable?	Yes	Sometimes	No
15. Because of your tinnitus, is it difficult for you to read?	Yes	Sometimes	No
16. Does your tinnitus make you upset?	Yes	Sometimes	No
17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?	Yes	Sometimes	No
18. Do you find it difficult to focus your attention away from your tinnitus and on other things?	Yes	Sometimes	No
19. Do you feel that you have no control over your tinnitus?	Yes	Sometimes	No
20. Because of your tinnitus, do you often feel tired?	Yes	Sometimes	No
21. Because of your tinnitus, do you feel depressed?	Yes	Sometimes	No
22. Does your tinnitus make you feel anxious?	Yes	Sometimes	No
23. Do you feel that you can no longer cope with your tinnitus?	Yes	Sometimes	No
24. Does your tinnitus get worse when you are under stress?	Yes	Sometimes	No
25. Does your tinnitus make you feel insecure?	Yes	Sometimes	No

For interpretation of the THI score

Total score = (number or 'Yes' responses x4) + (number of 'Sometimes' responses x2) = …

Grade of handicap due to tinnitus

Grade	Score	Description
1	0 to 16	Slight: only heard in quiet environment, very easily masked. No interference with sleep or daily activities.
2	18 to 36	Mild: easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities.
3	38 to 56	Moderate: may be noticed, even in the presence of background or environmental noise, although daily activities may still be performed.
4	58 to 76	Severe: almost always heard, rarely, if ever, masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities. Quiet activities affected adversely.
5	78 to 100	Catastrophic: always heard, disturbed sleep patterns, difficulty with any activity

Newman CW, Jacobson., Spitzer, JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg,* 1996; 122:143-8

Appendix 4. Functional Level Scale

FLS-scale	Patient's subjective experience
Regarding my current state of *overall* function, *not just during attacks* (check the ONE that best applies):	
1	My dizziness has no effects on my activities at all
2	When I am dizzy, I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
3	When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.
4	I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.
5	I am unable to work, drive, or take care of my family. I am unable to do most of the active things that I used to do. Even essential activities must be limited. I am disabled.
6	I have been disabled for one year or longer and/or I receive compensation (money) because of my dizziness or balance problem.

Appendix 5. Dizziness Handicap Inventory

P1. Does looking up increase your problem?	o Yes o Sometimes o No
E2. Because of your problem, do you feel frustrated?	o Yes o Sometimes o No
F3. Because of your problem, do you restrict your travel for business or recreation?	o Yes o Sometimes o No
P4. Does walking down the aisle of a supermarket increase your problems?	o Yes o Sometimes o No
F5. Because of your problem, do you have difficulty getting into or out of bed?	o Yes o Sometimes o No
F6. Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	o Yes o Sometimes o No
F7. Because of your problem, do you have difficulty reading?	o Yes o Sometimes o No
P8. Does performing more ambitious activities such as sports, dancing, household chores (sweeping or putting dishes away) increase your problems?	o Yes o Sometimes o No
E9. Because of your problem, are you afraid to leave your home without having without having someone accompany you?	o Yes o Sometimes o No
E10. Because of your problem have you been embarrassed in front of others?	o Yes o Sometimes o No
P11. Do quick movements of your head increase your problem?	o Yes o Sometimes o No
F12. Because of your problem, do you avoid heights?	o Yes o Sometimes o No
P13. Does turning over in bed increase your problem?	o Yes o Sometimes o No
F14. Because of your problem, is it difficult for you to do strenuous homework or yard work?	o Yes o Sometimes o No

E15. Because of your problem, are you afraid people may think you are intoxicated?	o Yes o Sometimes o No
F16. Because of your problem, is it difficult for you to go for a walk by yourself?	o Yes o Sometimes o No
P17. Does walking down a sidewalk increase your problem?	o Yes o Sometimes o No
E18.Because of your problem, is it difficult for you to concentrate	o Yes o Sometimes o No
F19. Because of your problem, is it difficult for you to walk around your house in the dark?	o Yes o Sometimes o No
E20. Because of your problem, are you afraid to stay home alone?	o Yes o Sometimes o No
E21. Because of your problem, do you feel handicapped?	o Yes o Sometimes o No
E22. Has the problem placed stress on your relationships with members of your family or friends?	o Yes o Sometimes o No
E23. Because of your problem, are you depressed?	o Yes o Sometimes o No
F24. Does your problem interfere with your job or household responsibilities?	o Yes o Sometimes o No
P25. Does bending over increase your problem?	o Yes o Sometimes o No

The patient is asked to answer each question as it pertains to dizziness or unsteadiness problems, specifically considering their condition during the last month. Questions are designed to incorporate functional (F), physical (P), and emotional (E) impacts on disability. To each item, the following scores can be assigned: No=0; Sometimes=2; Yes=4. Scores greater than 10 points should be referred to balance specialists for further evaluation; 16-34 Points (mild handicap); 36-52 Points (moderate handicap); 54+ Points (severe handicap)

Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1990;116: 424-427

Appendix 6. Search strategies

Central	1 MESH DESCRIPTOR Meniere Disease EXPLODE ALL AND CENTRAL:TARGET 2 (meniere* OR meniere's OR menieres):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 4 #1 OR #2 OR #3 5 MESH DESCRIPTOR Betahistine EXPLODE ALL AND CENTRAL:TARGET 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 7 #5 OR #6 8 #4 AND #7 9 MESH DESCRIPTOR Meniere Disease EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET 10 #8 OR #9
Medline (Ovid)	1 exp Endolymphatic Hydrops/ 2 (meniere* or meniere's or menieres).ab,ti. 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).ab,ti. 4 1 or 2 or 3 5 exp Betahistine/ 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL).ab,ti. 7 5 or 6 8 4 and 7 9 randomized controlled trial.pt 10 controlled clinical trial.pt. 11 randomized.ab. 12 placebo.ab. 13 drug therapy.fs. 14 randomly.ab. 15 trial.ab. 16 groups.ab. 17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18 exp animals/ not humans.sh. 19 17 not 18 20 8 and 19

Embase (Ovid)	1 exp Meniere disease/ 2 (meniere* or meniere's or menieres).ab,ti. 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).ab,ti. 4 1 or 2 or 3 5 exp betahistine/ 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL).ab,ti. 7 5 or 6 8 4 and 7 9 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 10 (control* adj group*).tw. 11 (trial* and (control* or comparative)).tw. 12 ((blind* or mask*) and (single or double or triple or treble)).tw. 13 (treatment adj arm*).tw. 14 (control* adj group*).tw. 15 (phase adj (III or three)).tw. 16 (versus or vs).tw. 17 rct.tw. 18 crossover procedure/ 19 double blind procedure/ 20 single blind procedure/ 21 randomization/ 22 placebo/ 23 exp clinical trial/ 24 parallel design/ 25 Latin square design/ 26 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 28 exp human 29 27 not 28 30 26 not 29 31 8 and 30

Web of Science (Web of Knowledge)	1 exp Meniere disease/ 2 (meniere* or meniere's or menieres).ab,ti. 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).ab,ti. 4 1 or 2 or 3 5 exp betahistine 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL).ab,ti. 7 5 or 6 8 4 and 7 9 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 10 (control* adj group*).tw. 11 (trial* and (control* or comparative)).tw. 12 ((blind* or mask*) and (single or double or triple or treble)).tw. 13 (treatment adj arm*).tw. 14 (control* adj group*).tw. 15 (phase adj (III or three)).tw 16 (versus or vs).tw. 17 rct.tw. 18 crossover procedure/ 19 double blind procedure/ 20 single blind procedure/ 21 randomization/ 22 placebo/ 23 exp clinical trial/ 24 parallel design/ 25 Latin square design/ 26 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 28 exp human/ 29 27 not 28 30 26 not 29 31 8 and 30

Register	1 MESH DESCRIPTOR Meniere Disease EXPLODE ALL AND INREGISTER 2 (meniere* OR meniere's OR menieres):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 4 #1 OR #2 OR #3 5 MESH DESCRIPTOR Betahistine EXPLODE ALL AND INREGISTER 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 7 #5 OR #6 8 #4 AND #7 9 MESH DESCRIPTOR Meniere Disease EXPLODE ALL WITH QUALIFIER DT AND INREGISTER 10 #8 OR #9
Clinicaltrials.gov	(meniere's OR menieres OR (ENDOLYMPHATIC AND HYDROPS) OR (LABYRINTH AND HYDROPS) OR (LABYRINTH AND SYNDROME) OR (aural AND vertigo) OR (labyrinth AND vertigo) OR (cochlea AND hydrops)) AND (BETAHISTINE OR BETAHISTINA OR BETAISTINA OR SERC OR AEQUAMEN OR BETASERC OR BETASERK OR BEATSERKA OR EXTOVYL OR FIDIUM OR LECTIL OR LOBIONE OR MEGINALISK OR MELOPAT OR MENIACE OR MERISLON OR MICROSER OR RIBRAIN OR VASOMOTAL) via Cochrane Regiter of Studies 1 BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL AND INSEGMENT 2 nct* AND INSEGMENT 3 #1 AND #2
ICTRP	meniere's AND betahistin* OR meniere* AND betahistin* OR meniere's AND serc OR meniere* AND serc OR meniere's AND betaserc OR meniere* AND betaserc

LILACS	Controlled Clinical Trials (TW:meniere's OR TW:menieres OR (TW:ENDOLYMPHATIC AND TW:HYDROPS) OR (TW:LABYRINTH AND TW:HYDROPS) OR (TW:LABYRINTH AND TW:SYNDROME) OR (TW:aural AND TW:vertigo) OR (TW:labyrinth AND TW:vertigo) OR (TW:cochlea AND TW:hydrops)) AND (TW:BETAHISTINE OR TW:BETAHISTINA OR TW:BETAISTINA OR TW:SERC OR TW:AEQUAMEN OR TW:BETASERC OR TW:BETASERK OR TW:BEATSERKA OR TW:EXTOVYL OR TW:FIDIUM OR TW:LECTIL OR TW:LOBIONE OR TW:MEGINALISK OR TW:MELOPAT OR TW:MENIACE OR TW:MERISLON OR TW:MICROSER OR TW:RIBRAIN OR TW:VASOMOTAL OR TW:beta-Histina)

Appendix 7. Staging of definite and certain Menière's disease

Stage	Four-tone average (dB)
1	**≤25**
2	**26 to 40**
3	**41 to 70**
4	**>70**

Staging is based on the four-tone average (arithmetic mean rounded to the nearest whole number) of the pure-tone thresholds at 0.5 kHz, 1 kHz, 2 kHz and 3 kHz of the worst audiogram during the interval six months before treatment. This is the same audiogram that is used as the baseline evaluation to determine hearing outcome from treatment. Staging should be applied only to cases of definite or certain Menière's disease.

Contributions of authors

All authors were involved in the drafting of the protocol.

Babette van Esch: BE selected and obtained studies, extracted data and assessed risk of bias. BE entered data into RevMan 5 and carried out and interpreted the analyses. BE drafted the final review and has responsibility for updating and maintaining the review.

Hester J Van der Zaag-Loonen: HZ selected studies, extracted data, assessed risk of bias and helped interpret the analyses. HZ provided advice throughout the analyses and drafted the final review.

Tjasse Bruintjes: TB provided advice and drafted the final review.

Louisa Murdin: LM provided advice and drafted the final review.

Adrian James: AJ provided advice and drafted the final review.

Peter Paul van Benthem: PB initiated the revision of the review, provided advice and drafted the final review.

Declarations of interest

Babette van Esch: none known.
Tjasse Bruintjes: none known.
Hester J Van der Zaag-Loonen: none known.
Louisa Murdin: none known.
Adrian James: none known.
Peter Paul van Benthem: none known.