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[Intervention Review]

Betahistine for Ménière's disease or syndrome

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ABSTRACT

Background

This is an update of a Cochrane Review first published in *The Cochrane Library* in Issue 1, 2001 and previously updated in 2008.

Ménière's disease is characterised by attacks of hearing loss, tinnitus and disabling vertigo. Betahistine (Serc[®], Betaserc[®]) is used by many people to reduce the frequency and severity of these attacks but there is conflicting evidence relating to its effects.

Objectives

The objective of this review was to assess the effects of betahistine in people with Ménière's disease.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP; and additional sources for published and unpublished trials. The date of the most recent search was 25 November 2010, following a previous update search in June 2007.

Selection criteria

Randomised controlled studies of betahistine versus placebo in Ménière's disease.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Study authors were contacted for further information.

Main results

Seven trials involving 243 patients were included. No trial met the highest quality standard set by the review because of inadequate diagnostic criteria or methods, and none assessed the effect of betahistine on vertigo adequately. Most trials suggested a reduction of vertigo with betahistine and some suggested a reduction in tinnitus but all these effects may have been caused by bias in the methods. One trial with good methods showed no effect of betahistine on tinnitus compared with placebo in 35 patients. None of the trials showed any effect of betahistine on hearing loss. No serious adverse effects were found with betahistine.

Authors' conclusions

There is insufficient evidence to say whether betahistine has any effect on Ménière's disease.

PLAIN LANGUAGE SUMMARY

Betahistine for Ménière's disease or syndrome

[Betahistine for Ménière's disease or syndrome \(Review\)](#)

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Ménière's disease is a disorder of the inner ear which results in a spinning form of dizziness (vertigo), hearing loss and ringing in the ear (tinnitus), and can be disabling. It has no known cause. When it is secondary to a known inner ear disorder, it is called Ménière's syndrome. Both can be difficult to diagnose. The drug betahistine hydrochloride (Serc[®], Betaserc[®]) has been used to reduce the frequency and severity of the attacks. While the drug is very acceptable to those who use it, the review of trials did not find enough evidence to show whether it is helpful. Further research is needed.

BACKGROUND

This is an update of a Cochrane Review first published in *The Cochrane Library* in Issue 1, 2001 and previously updated in 2008.

Prosper Ménière gave his name to a disorder of the inner ear characterised by recurrent episodes of spontaneous vertigo, fluctuating hearing loss and tinnitus, often with a feeling of fullness in the ear. The disorder may be subdivided into two categories. It is usually idiopathic (i.e. without known cause), in which case it is referred to as Ménière's disease. It may also be secondary to a number of established inner ear disorders, in which case it is referred to as Ménière's syndrome.

Ménière's disease is most common between 40 and 60 years of age, although younger people can also be affected. The incidence is estimated to be between 50 and 350 per hundred thousand per year (Stahle 1978; Watanabe 1983). Acute episodes of Ménière's tend to occur in clusters with a mean frequency of between six and 11 clusters per year, though remission may last several months (Friberg 1984). Episodes have been observed to occur with increasing frequency over the first few years after presentation and then decrease in association with a sustained deterioration in hearing (Moffat 1997). In most cases, vertiginous episodes eventually cease completely (Silverstein 1989). The fluctuating, progressive and unpredictable natural history of Ménière's makes investigation of any treatment effect difficult.

Ménière's is associated with endolymphatic hydrops, i.e. raised endolymph pressure in the membranous labyrinth of the inner ear (Hallpike 1938). The cause of the hydrops is not known in most cases. Specific disorders affecting the inner ear which are associated with hydrops include temporal bone fracture, syphilis, hypothyroidism, Cogan's syndrome and Mondini dysplasia. A direct causal relationship between Ménière's and endolymphatic hydrops remains unproven (Ruckenstein 1999).

The disorder is not always easy to diagnose and there is no 'gold standard' diagnostic test. It is almost certainly over-diagnosed by non-specialists. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines (Alford 1972) which have been revised twice (Committee 1995; Pearson 1985), but they are not universally accepted. Nevertheless, they provide a standard which can be applied easily in normal clinical practice. In brief, these guidelines now stipulate that a 'definite' diagnosis can only be made on the basis of at least two spontaneous episodes of rotational vertigo lasting at least 20 minutes, audiometric confirmation of a sensorineural hearing loss, plus tinnitus and/or a perception of aural fullness. These criteria exclude most other vestibular conditions, but further investigation is also necessary to exclude other pathologies.

Ideally, the aim of treatment is:

1. to reduce the number and severity of acute attacks of vertigo;
2. to abort or ameliorate hearing loss and tinnitus associated with such attacks;
3. to alleviate any chronic symptoms (e.g. tinnitus and imbalance); and
4. to prevent progression of the disease, in particular the loss of hearing and balance function which characterise the disorder.

No single treatment modality has been shown to achieve all these aims.

It has been suggested that betahistine hydrochloride reduces the frequency and severity of vertiginous episodes and tinnitus and arrests the progression of hearing loss in patients with Ménière's syndrome (Solvay 1998). The mechanism of action of the drug may be the reduction of endolymphatic pressure through improved microvascular circulation in the stria vascularis of the cochlea (Martinez 1972) or inhibition of activity in the vestibular nuclei (Timmerman 1994). Betahistine hydrochloride is also referred to as betahistine dihydrochloride. Betahistine mesylate, dimesylate and maleate are alternative formulations. Betahistine is also known as betahistidine (and equivalent names in other languages). Proprietary names for betahistine include Aequamen[®], Betaserc[®], Betaserk[®], Betaserka[®], Extovyl[®], Fidium[®], Lectil[®], Lobione[®], Meginalisk[®], Melopat[®], Meniace[®], Merislon[®], Microser[®], Ribrain[®], Serc[®] and Vasomotal[®] (Martindale 1996).

OBJECTIVES

This review aims to assess the effects of betahistine compounds in patients with either Ménière's disease or Ménière's syndrome. Its effect on the frequency and severity of the acute attacks, on chronic symptoms such as tinnitus, imbalance and hearing loss and on the progression or deterioration of these symptoms is assessed.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled trial of betahistine versus placebo. Trials analysed on an intention-to-treat basis were preferred, and where necessary and possible we reconstructed intention-to-treat analyses. We only included cross-over trials if data from results before the cross-over were extractable. This avoided the potential confounding effect of a carry-over phenomenon.

Types of participants

Patients of any age with Ménière's disease or syndrome. We graded the diagnostic accuracy of studies on the basis of the robustness of the methods used to diagnose these disorders and this grading formed the basis of a sensitivity analysis. We graded studies in which the American Academy of Otolaryngology - Head and Neck Surgery 1995 criteria were used and only patients with 'definite' or 'certain' Ménière's included in the study (I). We graded studies in which clear but less rigorous criteria were used (II). We graded studies in which no, or less clear, diagnostic criteria were given (III). Studies distinguishing patients with Ménière's disease from those with Ménière's syndrome were to be considered separately. Trials studying patients who had not previously received betahistine were to be distinguished from those in which patients may have received betahistine in the past.

Types of interventions

Betahistine versus placebo.

We decided to compare betahistine with placebo as no 'gold-standard' treatment for Ménière's is available. Comparisons with other drugs have not been made as their effects on the condition

have not been formally assessed. Further comparisons may be carried out in future reviews.

Concurrent use of other medication was acceptable if used equally in each group.

Types of outcome measures

Important outcomes are differences in the following.

1. Number and severity of acute attacks of vertigo.
2. Hearing.
3. Severity of tinnitus.
4. Perception of aural fullness.
5. Functional impairment and disability.
6. Overall well being and quality of life.
7. Side effects.

In patients with bilateral and asymmetric disease, we assessed outcomes 2, 3 and 4 using the more severely affected ear. Outcomes were measured in the short or long-term. The prevention of a progressive hearing loss is equally important but must be measured over a period of many months or years.

Given the chronic nature of Ménière's disease and the fluctuating and episodic pattern of the symptoms the long-term effectiveness of any therapy is extremely important. Ideally, trials would evaluate both the long-term (> three months) effects of short courses of treatment (two to 12 weeks) and the effectiveness of long-term (> three months) treatment. It may be difficult to draw firm conclusions about the applicability of the short-term results of short courses of treatment. Ideally, longer-term outcomes should be assessed, for example, at 18 to 24 months and 24 to 48 months after onset of treatment, as suggested by the AAO-HNS. However, it is unlikely that placebo-controlled drug trials will last this long.

The severity of the disease and the time elapsed since its onset could be an important factor in determining response to betahistine, and we will attempt to develop an appropriate staging system to address this issue in more detail.

The AAO-HNS 1995 guidelines for the evaluation of treatment of Ménière's disease are designed to evaluate the long-term effects of a specific (usually surgical) intervention. However, like the diagnostic criteria referred to above, they are well defined and rigorous. In outline, the number of vertiginous episodes per unit time is recorded before and after treatment. Hearing is assessed audiotically using the average of pure tone thresholds at 0.5, 1, 2 and 3 kHz. Functional impairment is assessed with a scale measuring impairment of daily tasks. Measures for assessing tinnitus, the perception of aural fullness and intensity of vertigo have not been defined.

We categorised the quality of outcome measures used in each study on the basis of their similarity to the AAO-HNS guidelines. We graded studies using similar measures (I), dissimilar but appropriate measures (II), and those using measures considered inadequate (III). This also formed the basis for a sensitivity analysis.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication

status restrictions. The date of the last search was 25 November 2010, following a previous search update in June 2007.

Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; mRCT; ClinicalTrials.gov; ICTRP and Google.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with 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 5.0.2, Box 6.4.b. (*Handbook* 2009)). Search strategies for major databases including CENTRAL are provided in [Appendix 1](#).

Searching other resources

We scanned reference lists of identified studies for further trials. We searched PubMed, TRIPdatabase, NHS Evidence - ENT and Audiology, and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials. For the previous searches in June 2007, the authors' own files were scanned for relevant studies and we contacted manufacturers of betahistine for unpublished trials ([Appendix 2](#)).

Data collection and analysis

Selection of studies

One author scanned the initial search results to identify trials which loosely met the inclusion criteria. Both authors then reviewed the full-text articles of the retrieved trials and applied the inclusion criteria independently. Any differences in opinion about which studies to include in the review were resolved by discussion between the two authors. The authors were blind to the names of journals, authors and the study results while applying the criteria for determining which studies to include in the review.

Data extraction and management

The two authors independently extracted data from the studies using standardised data forms. We extracted data so as to allow an intention-to-treat analysis. Where necessary and where sufficient data from the study were not provided, we wrote to the authors of the study requesting further information ([Frew 1976](#) via co-author Menon; [Meyer 1985](#); [Mira 2003](#); [Okamoto 1968](#); [Oosterveld 1984](#); [Oosterveld 1989](#); [Ricci 1987](#); [Salami 1984](#); [Schmidt 1992](#); [Wilmot 1976](#)).

Assessment of risk of bias in included studies

The two authors independently assessed the quality of all included trials using a modification of the method derived by Schulz et al ([Schulz 1995](#)). We resolved differences by discussion. We assessed the selected studies for the following characteristics:

1. the certainty of diagnosis of Ménière's (see '[Types of participants](#)');

2. the adequacy of the randomisation process and of allocation concealment;
3. the potential for attrition bias after allocation to study group, i.e. losses to follow up and whether analysis was by intention-to-treat;
4. whether the trial was conducted and outcome assessed in a double-blind manner;
5. the adequacy of compliance and its assessment; and
6. the quality of the outcome assessment (see '[Types of outcome measures](#)').

We graded studies A, B or C for their overall quality. This score is derived from (a) the individual grade for characteristics 1 and 6 (according to the criteria given above) and (b) methodological quality (characteristics 2, 3, 4 and 5).

Grade A: Diagnostic accuracy grade I and outcome quality grade I and low risk of bias in methodology.

Grade B: Diagnostic accuracy grade I or II and/or outcome quality grade I or II and/or medium risk of bias in methodology.

Grade C: Diagnostic accuracy grade III and/or outcome quality grade III and/or high risk of bias in methodology.

Data synthesis

Data analysis was by intention-to-treat when possible. We measured study outcomes in a variety of ways using continuous, discrete and categorical variables. We dichotomised data where appropriate. We sought statistical advice to determine the best way of presenting and summarising the data.

In the future, if comparable data of sufficient quality (overall grade A or B) become available, they will be combined to give a summary measure of effect. We will use study quality in a sensitivity analysis. We will also carry out subgroup analyses. This will be restricted to a very small number of subgroups, listed in advance and based on pathophysiologically plausible differences in response. The boundaries defining inclusion and exclusion will also be clearly specified in advance and a significance test for interaction with the treatment effect will be performed. Examples of possible subgroups include groups defined by duration and severity of disease and different doses of betahistine.

RESULTS

Description of studies

Results of the search

From the 2010 update searches we retrieved a total of 98 references; 56 of these were removed in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 42 references for further consideration. Only one was placebo-controlled and this did not comply with the review inclusion criteria ([Redon 2010](#)).

In previous searches, we identified 67 clinical trials of betahistine, but only 21 were placebo-controlled and only seven complied with the inclusion criteria of the review.

Included studies

Seven studies are included in the review (see also [Characteristics of included studies](#)). These are:

[Burkin 1967](#)

[Elia 1966](#)

[Mira 2003](#)

[Okamoto 1968](#)

[Ricci 1987](#)

[Salami 1984](#)

[Schmidt 1992](#)

Participants

Six trials studied patients with a diagnosis of Ménière's disease only. [Burkin 1967](#), [Elia 1966](#) and [Salami 1984](#) referred to the condition as Ménière's syndrome, but do not describe any underlying abnormality. They appear to be describing patients with Ménière's disease. In [Mira 2003](#) both Ménière's disease and benign positional paroxysmal vertigo (BPPV) patients were studied, but results were presented separately for each outcome.

The seven trials recruited a total of 243 patients but 22 patients withdrew. The smallest studied 10 ([Ricci 1987](#)) and the largest 81 ([Mira 2003](#)). Diagnostic criteria varied, with only [Mira 2003](#) using AAO-HNS guidelines to establish a diagnosis of "probable or possible Ménière's disease". The other six studies did not use the AAO-HNS guidelines, though full criteria were described by [Schmidt 1992](#). [Elia 1966](#) stated that all patients had intractable vertigo for at least four months before the trial, and [Schmidt 1992](#) that all patients had an exacerbation in the preceding month. No studies excluded patients who had received betahistine previously, though [Schmidt 1992](#) excluded those who received betahistine 16 mg three times daily or more within the previous three months. [Mira 2003](#), [Ricci 1987](#), [Salami 1984](#) and [Schmidt 1992](#) excluded patients in whom betahistine was contra-indicated. The exclusion criteria in [Mira 2003](#) included concomitant infectious, definite cerebrovascular disease and concomitant therapy with anti-vertigo drugs. [Salami 1984](#) and [Schmidt 1992](#) excluded patients whose vertigo was thought to be non-vestibular. [Schmidt 1992](#) listed the reasons for not including 68 potential recruits in the trial. Exclusion criteria were not defined in the other three studies.

Intervention

All studies compared betahistine hydrochloride with placebo. [Schmidt 1992](#) used a slow-release formulation. Most early studies used smaller doses of betahistine ([Burkin 1967](#) and [Elia 1966](#) 4 mg four times daily, [Okamoto 1968](#) 18 mg twice daily, [Ricci 1987](#) and [Salami 1984](#) 8 mg three times daily, [Schmidt 1992](#) 24 mg three times daily). The most recent study, [Mira 2003](#), used 16 mg twice daily.

Allocation

All studies were randomised.

Trial design

All were double-blind. The studies by [Burkin 1967](#), [Elia 1966](#) and [Schmidt 1992](#) were cross-over trials, but results could be analysed up to the time of cross-over. Data were published from a two-week period by [Burkin 1967](#), [Elia 1966](#) and [Okamoto 1968](#), six weeks by [Salami 1984](#), at baseline, 15, 30, 60 and 90 days by [Mira 2003](#) and at monthly intervals up to 16 weeks by [Schmidt 1992](#). [Ricci 1987](#) set the duration of the trial for each patient as being up to 10 times the mean interval between attacks of Ménière's for that patient.

Outcome measures

Short-term results were published by [Burkin 1967](#), [Elia 1966](#), [Okamoto 1968](#), [Salami 1984](#) and [Schmidt 1992](#). Longer-term results were published by [Mira 2003](#), [Ricci 1987](#) (up to 40 weeks) and [Schmidt 1992](#).

1) Vertigo

[Salami 1984](#), [Ricci 1987](#) and [Mira 2003](#) recorded the nature, duration, intensity and number of attacks. [Salami 1984](#) recorded this at weekly intervals, [Ricci 1987](#) monthly and [Mira 2003](#) at baseline, 15, 30, 60 and 90 days. [Mira 2003](#) used a composite self-rating scale, incorporating values for intensity (four-point scale: 0 = absent, 1 = mild, 2 = severe, 3 = disabling), duration (five-point scale: 0 = none, 1 = < 1 minute, 2 = < 15 minutes, 3 = some hours, 4 = ≥ 1 day) and associated symptoms (nausea and vomiting) (three-point scale: 0 = absent, 1 = nausea, 2 = vomiting). [Salami 1984](#) used a simple scoring system to record severity of vertigo (absent = 0, mild = 1, moderate = 2, severe = 3). The same four-point system was used by [Elia 1966](#) over a two-week period. [Okamoto 1968](#) used a three-point scale over a two-week period (absent = 0, possible to walk with support = 1, unable to stand = 2). [Schmidt 1992](#) measured the number and intensity of attacks of imbalance (not true vertigo) at weekly intervals. The results were published as an 'imbalance score' which is a product of a weighted value of severity (mild = 1, moderate = 4, severe = 9) and frequency. [Burkin 1967](#) simply questioned whether patients were still 'dizzy' after two weeks treatment.

2) Hearing

Pure-tone audiograms were recorded by [Salami 1984](#) every three weeks, [Schmidt 1992](#) every four weeks and [Ricci 1987](#) every month. All their published data were based on the four-tone average of the frequencies 0.25, 0.5, 1 and 2 kHz. [Okamoto 1968](#) checked audiograms at two weeks and graded severity of hearing loss (< 20 dB = 0, 20 to 50 dB = 1, > 50 dB = 2). Audiometric examinations were performed during the [Mira 2003](#) study using the four-tone average, but results were only partially analysed and not mentioned in the study report (personal communication, [Mira 2003](#)).

3) and 4) Tinnitus and aural fullness

[Salami 1984](#) used a seven-point scale to assess these symptoms every week (none, rare, occasionally, frequently without inconvenience, constantly with inconvenience, constantly and troubling, impairing life and normal relationships). [Ricci 1987](#) used the same scale for aural fullness, and a similar scale for tinnitus at monthly intervals. [Schmidt 1992](#) scored tinnitus and fullness (absent = 0, mild = 2, moderate = 4 or severe = 6) every week. [Elia 1966](#) recorded severity of tinnitus after two weeks with a similar four-point scale. [Okamoto 1968](#) recorded tinnitus severity at two weeks with a three-point scale (absent = 0, only heard in silence = 1, heard over background noise = 2). Tinnitus and aural fullness were not evaluated in [Mira 2003](#).

5) and 6) Functional impairment/disability/quality of life

These measures were not addressed directly in the majority of the studies, but [Salami 1984](#) and [Ricci 1987](#) recorded whether aural fullness was impairing life and normal relationships and [Salami 1984](#) the same for tinnitus. The composite self-rating scale used in [Mira 2003](#) included a score for quality of life (three-point scale:

0 = normal, 1 = partial inactivity, 2 = total inactivity) (personal communication, [Mira 2003](#)).

7) Side effects

All trials monitored patients for subjective side effects.

Individual patient data were published by [Burkin 1967](#), [Elia 1966](#) and [Okamoto 1968](#). Summarised data were provided in the other studies. [Salami 1984](#) added the symptom scores for each group at zero, three and six weeks and used Fisher's test to identify significant differences. [Schmidt 1992](#) applied the Wilcoxon matched-pairs test to mean monthly symptom scores to identify significant differences.

Excluded studies

We excluded a total of 15 studies from the review (see [Characteristics of excluded studies](#)).

Participants

In the following studies, patients with balance or vestibular disorders other than Ménière's were included as well as those with the disorder. Results for patients with Ménière's could not be extracted for separate analysis:

[Canty 1981](#)
[Conraux 1988](#)
[Fischer 1985](#)
[Legent 1988](#)
[Oosterveld 1989](#)
[Singarelli 1979](#)

We excluded [Solvay 2007](#) and [Redon 2010](#) because all patients were post-surgical: they had all undergone vestibular neurectomy for disabling Ménière's disease and had confirmed vestibular areflexia.

Allocation

Allocation of patients to betahistine or placebo was not randomised in these studies. In both, placebo was administered to all patients for two weeks after a two-week course of betahistine:

[Hicks 1967](#)
[Wolfson 1967](#)

Trial design

The following studies were cross-over trials and results before cross-over are not available:

[Frew 1976](#)
[Meyer 1985](#)
[Oosterveld 1984](#)
[Watanabe 1967](#)
[Wilmot 1976](#)

Risk of bias in included studies

The studies are of variable methodological rigour.

1) Certainty of diagnosis

Grade I

No studies used the AAO-HNS guidelines to make a diagnosis of 'definite' Ménière's or 'certain' Ménière's. The former requires post-mortem confirmation.

Grade II

Schmidt 1992 used a clearly defined set of criteria based on the definition of Ménière's used at the University Hospital Utrecht (no reference available). A description of the diagnostic protocol shows that comprehensive measures were taken to exclude non-Ménière's patients. There is no clear statement that the patients suffered 'two or more spontaneous episodes of rotational vertigo lasting at least 20 minutes', otherwise the study would have been allocated diagnostic accuracy grade I.

Grade III

Burkin 1967, Ricci 1987 and Salami 1984 gave a standard clinical definition of Ménière's in the introduction to their papers but did not clearly describe the application of diagnostic inclusion or exclusion criteria. Salami 1984 excluded patients with vertigo thought to be of non-vestibular origin or those previously exposed to ototoxic drugs. Burkin 1967 based diagnosis on a description by Beeson 1963. Elia 1966 based diagnosis on a description by Williams 1964 which does not include the presence of tinnitus or aural fullness as a salient feature. No other description of diagnostic or exclusion criteria for Ménière's was given. Two patients did not experience tinnitus during the study, which questions the accuracy of diagnosis. Okamoto 1968 based diagnosis on history, hearing examination and vestibular function testing but did not give details or a definition. Individual patient data were published and this shows that only eight of the 36 patients had the triad of vertigo with tinnitus and hearing loss before or during the trial. Retrospective application of AAO-HNS criteria allows a diagnosis of possible Ménière's disease in 16 patients (nine received betahistine and seven placebo). Mira 2003 stated that a diagnosis of only "probable or possible Ménière's disease" was made, using the AAO-HNS criteria.

2) Allocation bias

Low risk of bias

In Elia 1966 allocation was on an alternate patient basis but as provision of betahistine or placebo was strictly double-blind, randomisation is considered satisfactory. Ten patients were placed in each group. Significant baseline differences were present: pre-trial symptom scores were worse in the betahistine group.

Allocation was from a table of random numbers by an independent person not otherwise connected with the trial by Okamoto 1968. It was implied that randomisation was concealed. Twenty patients were placed in each group and pre-trial symptom scores were similar in each group.

In Mira 2003 two randomised lists (one for Ménière's disease and one for BPPV) were generated centrally by the Medical Department of the pharmaceutical company that supplied the drug and placebo tablets, using Fisher and Yates random number tables. The study investigators assigned the study admission numbers "corresponding to the progressive number reported in the related randomization list (i.e. according to the two diagnoses)"

to the participants (personal communication, Mira 2003). The percentages of patients using concomitant therapies (withdrawn seven days before the start of the trial), and who had used previous anti-vertigo treatments were both slightly higher in the betahistine group than in the placebo group (Ménière's disease and BPPV subgroups combined).

Medium risk of bias

Allocation was randomised by Schmidt 1992, but the method was not described. The author distinguished between true randomisation and 'pseudorandomisation' (e.g. alternate allocation, allocation by date) so implying the use of an acceptable method in this study. It was not stated whether randomisation was concealed. It is inferred that 20 patients were allocated to each group. Treatment and placebo groups were similar in age, sex, duration of disease, and bi/uni-laterality of disease. There were no significant differences in symptom scores between the two groups.

In Ricci 1987 allocation was from a randomisation list. It was not stated whether randomisation was concealed. Five patients were placed in each group. The sex, age, disease duration and interval between vertiginous episodes were similar in each group.

In Salami 1984 allocation was described as completely randomised and into balanced groups but the method was not stated. Fifteen patients were allocated to each group. At the start of the trial there was no significant difference between patients in the treatment and placebo groups for sex, age, weight or time since diagnosis and symptom scores were similar.

In Burkin 1967 allocation was described as randomised, but the method was not stated. It is not clear whether randomisation was concealed. Eleven patients were allocated to each group. The age, sex and duration of current episode of vertigo were similar in each group.

High risk of bias

No study described an inadequate randomisation method and studies not using randomisation were excluded by the protocol.

3) Attrition bias

Low risk of bias

Schmidt 1992 described the circumstances leading to withdrawal from the trial by five patients. A further three patients violated the trial protocol but were included by the intention-to-treat principle. No patients withdrew from the trial by Salami 1984 (personal communication).

Medium risk of bias

Eighteen out of 20 patients completed two weeks of the trial by Elia 1966. Seven patients received betahistine and nine placebo. Two patients withdrew in the first phase of this trial (one not tolerating side effects from placebo, the other moving out of the area). Outcome data are not provided up to the point of withdrawal so an intention-to-treat analysis cannot be performed, but these drop-outs are unlikely to significantly affect the results.

Thirty-two out of 144 patients (Ménière's disease and BPPV patients combined) did not complete the study in Mira 2003; 18 from the betahistine group and 14 from the placebo group (personal communication). Although an 'intention-to-treat'

analysis is presented in the published paper, in fact 81 Ménière's disease patients were randomised but only 72 were analysed. The trial authors' 'intention-to-treat' analysis incorporates a 'last observation carried forward' approach, whereby last observation data for patients who dropped out of the study in the second month (and for all other cases with missing data at the third month) was carried forward to the third month.

Two patients withdrew from each group in the study by [Okamoto 1968](#). No reasons are given in the study report, but this was due to subject convenience and not adverse effects ([Okamoto 1968](#), personal communication). Outcome data are not provided up to the point of withdrawal so an intention-to-treat analysis cannot be performed.

There is no mention of patients dropping out of two of the trials [Burkin 1967](#) and [Ricci 1987](#). It is therefore not known how many patients failed to complete these trials, if any, and what influence this might have had on outcome.

4) Blinding of trial

All studies were described as double-blind in performance and assessment.

5) Compliance

Compliance with medication was checked during the trial by [Schmidt 1992](#) but results are not published. Tablet bottles were collected during the trial by [Elia 1966](#) but it was not reported whether compliance was recorded. There is no mention of compliance in the other trials ([Burkin 1967](#); [Mira 2003](#); [Okamoto 1968](#); [Ricci 1987](#); [Salami 1984](#)).

6) Outcome assessment

Grade I

No studies complied fully with current AAO-HNS guidelines (see '[Types of outcome measures](#)'). Even though the guidelines from 1972 were used by [Ricci 1987](#) and [Salami 1984](#), data were published in summary form making optimal assessment of vertigo and hearing difficult. The summary of data on vertigo control which was published by [Ricci 1987](#) allows calculation of a numerical value for vertigo control in all but two out of 10 patients. The data provided by [Salami 1984](#) do not allow calculation of a numerical value, but data on frequency and intensity were provided.

[Ricci 1987](#), [Salami 1984](#) and [Schmidt 1992](#) used a four-tone average of lower frequency than current guidelines on hearing assessment but this is considered acceptable and adequate data were published to allow comparison between the two groups within each study.

Assessment of tinnitus and aural fullness is thought to be adequate in all studies when measured. These outcomes were not measured in [Mira 2003](#).

Simple recording of subjective side effects is considered acceptable in all studies.

Grade II

The recording of vertigo by [Elia 1966](#) made no distinction between intensity and severity. The grading systems for vertigo and audiological severity of hearing loss used by [Okamoto 1968](#) were

basic but are considered adequate. The number of vertigo attacks per month was assessed at baseline and other time points up to 90 days in [Mira 2003](#). Vertigo intensity was also measured at the same time points and the composite self-rating scale used in the study also incorporated a measure of impact on quality of life. However, results for hearing, which was assessed in the study using the four-tone average, were only partially analysed and not presented in the study report (personal communication, [Mira 2003](#)).

Grade III

[Schmidt 1992](#) questioned patients on 'imbalance' rather than spontaneous rotational vertigo. This is considered a less appropriate measure. [Burkin 1967](#) recorded 'dizziness' only. This is considered too imprecise to be an acceptable measure of vertigo.

One study ([Mira 2003](#)) assessed well being and quality of life using a three-point categorical scale (comprising normal activity, partial inactivity and total inactivity) as part of a composite self-rating system. The authors applied parametric statistical tests to these ordered categorical data, based on the allocation of numerical values to each of the three categories (values of 0, 1 and 2 respectively). This technique is considered inappropriate.

A summary of included study quality grading is set out in [Table 1](#).

Effects of interventions

The quality of the outcome measures used varied between studies (see '[Types of outcome measures](#)').

Short-term therapy (< three months)

1. Vertigo

Grade I outcome measure

[Salami 1984](#) reported a statistically significant benefit from betahistine over placebo in reduction of intensity ($P < 0.0001$) and frequency ($P < 0.01$) of attacks of vertigo. Individual patient data were not published.

[Mira 2003](#): At baseline participants had a mean number of vertigo attacks per month of 7.04 (SD 9.55) in the betahistine group and 5.88 (SD 7.16) in the placebo group (MD (mean difference) 1.16, 95% confidence interval (CI) -2.78 to 5.10). By one month a statistically significant reduction in the mean number of attacks in the betahistine group was recorded: 2.21 (SD 2.40) compared to 4.58 (SD 4.23) in the placebo group (MD -2.37, 95% CI -3.94 to -0.80). At three months the mean number of attacks was 2.29 (SD 3.02) in the betahistine group and 5.03 (SD 5.90) in the placebo group (MD -2.74, 95% CI -4.87 to -0.61). Results for vertigo intensity were similar. At baseline mean vertigo intensity scores in the betahistine group were 1.74 (SD 0.90) and 1.68 (SD 0.90) in the placebo group (MD 0.06, 95% CI -0.36 to 0.48). By one month the reduction in mean intensity score reached statistical significance in the betahistine group: 0.88 (SD 0.64) compared to 1.24 (SD 0.85) in the placebo group (MD -0.36, 95% CI -0.71 to -0.01). At three months (the close of the trial) the difference between groups was more pronounced: 0.71 (SD 0.80) in the betahistine group compared to 1.26 (SD 0.79) in the placebo group (MD -0.55, 95% CI -0.92 to -0.18) (additional data from personal communication, [Mira 2003](#)).

Grade II outcome measure

Elia 1966: At the start of the trial, six out of seven had severe vertigo in the betahistine group, compared with six out of nine on placebo. All patients receiving betahistine improved. One patient deteriorated from mild to severe on placebo, and none improved on placebo.

Okamoto 1968: In the betahistine group, five patients had severe vertigo at the start, 10 had moderate vertigo and four had none. None of these 18 patients had vertigo while on betahistine for two weeks. The control group was similar at the start. Fourteen had no vertigo while taking placebo, one improved and two had no change in vertigo severity. Analysis of the subgroup of 16 patients considered to have a diagnosis consistent with Ménière's disease (see 'Certainty of diagnosis') suggests no beneficial effect of betahistine on vertigo (relative risk of being better = 1.17, 95% CI 0.86 to 1.58).

Grade III outcome measure

Burkin 1967: At the start of the trial all patients were dizzy. After two weeks of betahistine, five of 11 patients reported no dizziness. All 11 patients in the placebo group continued to experience dizziness at two weeks.

Schmidt 1992: Mean imbalance scores were higher in the betahistine group than the control group after one and two months of the trial. As the data are ordinal and individual patient data were not published, this result is difficult to interpret.

2. Hearing

Grade I outcome measure

Salami 1984 found no difference in hearing loss between the betahistine and placebo groups by six weeks.

Schmidt 1992 found no difference in hearing loss between the betahistine and placebo groups at one or two months.

Grade II outcome measure

Okamoto 1968: At the start of the trial, 13 patients in the betahistine group and nine in the control group had normal hearing on audiogram. Of those with a hearing loss, two improved on betahistine and one deteriorated, while one improved on placebo.

3. Tinnitus

Grade I outcome measure

Elia 1966: At the start of the trial, five out of seven had severe tinnitus in the betahistine group, compared with five out of nine on placebo. One patient in each group had no tinnitus throughout the trial. Of the remainder, all patients taking betahistine noted improvement in tinnitus compared with only three patients on placebo. Tinnitus became worse for one patient taking placebo.

Okamoto 1968: Severity of tinnitus was similar in each group at the start of the trial. It improved in nine patients on betahistine but only three on placebo. Analysis of the Ménière's subgroup (see 'Certainty of diagnosis') suggests no significant effect of betahistine (relative risk of being better = 2.4, 95% CI 0.11 to 51.32).

Salami 1984 found a statistically significant reduction in tinnitus with betahistine ($P < 0.001$).

Schmidt 1992 found no difference in tinnitus between the betahistine and placebo groups at one or two months.

4. Aural fullness

Grade I outcome measure

Salami 1984 found a statistically significant reduction in aural fullness with betahistine ($P < 0.02$).

Schmidt 1992 found no difference in aural fullness between the betahistine and placebo groups at one or two months.

5. Overall well being and quality of life

Grade III outcome measure

Mira 2003 reported a significant improvement in activity levels at two and three months in the betahistine group.

Side effects

Mira 2003: headache was reported more frequently in patients taking betahistine than placebo (5/41 versus 0/40). Side effects were no different in the betahistine group from the placebo group in any other study.

Long-term therapy (> three months)

1. Vertigo

Grade I outcome measure

Ricci 1987: Over a period 10 times longer than the previous interval between attacks of vertigo, three of five patients on betahistine experienced no vertigo. Two reported no change in vertigo and all five taking placebo reported no change. There was no significant beneficial effect of betahistine (relative risk of being better = 5.0, 95% CI 0.3 to 84).

Grade III outcome measure

Schmidt 1992: Imbalance was greater in the betahistine group than the placebo group at four months but MANOVA testing found this not to be statistically significant ($P = 0.6$). There was a significant improvement in imbalance in both groups ($P = 0.001$).

2. Hearing

Grade I outcome measure

Ricci 1987: The audiogram of one patient improved to normal while taking betahistine (no information is given on the hearing loss at the start of the trial). No change in hearing was noted in any other patient on betahistine or placebo.

Schmidt 1992 found no difference in hearing loss between the betahistine and placebo groups over four months.

3. Tinnitus

Grade I outcome measure

Ricci 1987: All 10 patients had tinnitus and none reported improvement on betahistine or placebo.

Schmidt 1992 found no difference in tinnitus between the betahistine and placebo groups over four months.

4. Aural fullness

Grade I outcome measure

[Ricci 1987](#): Seven of the 10 patients had aural fullness and none of them reported improvement on betahistine or placebo.

[Schmidt 1992](#) found no difference in aural fullness between the betahistine and placebo groups over four months.

Summary of results

The heterogeneous nature of the studies, in particular regarding the dosage and duration of betahistine and the outcome measures used, makes it difficult to summarise the results. A statistical summary is not possible.

Vertigo

[Schmidt 1992](#) did not assess vertigo but found no greater reduction in imbalance from betahistine than from placebo. Imbalance improved significantly in both the placebo and betahistine groups. Studies with weaker methods showed a beneficial effect of betahistine on vertigo over short and long periods, though this was not confirmed by analysis of the Ménière's subgroup in the study by [Okamoto 1968](#). A statistically significant reduction in both mean number of vertigo attacks per month and mean vertigo intensity scores was found from one month onwards in [Mira 2003](#).

Hearing loss

[Schmidt 1992](#) and [Salami 1984](#) found no difference between betahistine and placebo. [Okamoto 1968](#) and [Ricci 1987](#) had similar findings.

Tinnitus

Tinnitus was not altered by betahistine in the study by [Schmidt 1992](#). Of the studies with weaker methods, the study by [Ricci 1987](#) and subgroup analysis in the study by [Okamoto 1968](#) also found no difference. [Elia 1966](#) and [Salami 1984](#) found tinnitus was reduced by betahistine.

Aural fullness

Aural fullness was not altered by betahistine in the [Schmidt 1992](#) study. [Ricci 1987](#) also found no difference from placebo, though there was a significant reduction with betahistine in the [Salami 1984](#) trial.

Quality of life

Only one study ([Mira 2003](#)) investigated an aspect of quality of life and interpretation of the results is problematic.

Side effects

Side effects were no different in the betahistine group from the placebo group in any study.

DISCUSSION

There is no high quality evidence on the effect of betahistine in Ménière's disease or syndrome.

We found no trials with a low risk of methodological bias which used the highest level of diagnostic criteria and outcome measures (i.e. overall quality grade A - see '[Data collection and analysis](#)'). Only

one trial was considered to have overall quality grade B ([Schmidt 1992](#)). As a result different trials could not be combined for a summary of effect. The other five included trials were allocated overall quality grade C because of their unclear or non-specific diagnostic criteria ([Burkin 1967](#); [Elia 1966](#); [Mira 2003](#); [Okamoto 1968](#); [Ricci 1987](#); [Salami 1984](#)). The lack of diagnostic certainty makes it inappropriate to combine results with the grade B study in either a meta-analysis or a sensitivity analysis. No trials specifically described results of treatment in patients with Ménière's syndrome.

There was no advantage in a slow release preparation of betahistine compared with placebo in the control of hearing loss, tinnitus or aural fullness in Ménière's disease by the grade B trial ([Schmidt 1992](#)) either in the short or long-term. Vertigo was not specifically assessed in this study. This was a parallel cross-over trial in which only 17 patients received betahistine in the first phase. None of the grade C trials found any change in hearing loss with betahistine though some suggest a beneficial effect on vertigo and tinnitus. Betahistine was well tolerated, though increase in headache compared with placebo was reported in one trial ([Mira 2003](#)).

The five grade C trials may have unintentionally included patients without a certain diagnosis of Ménière's disease, and therefore their results should be interpreted with caution. The diagnostic criteria in one were particularly unsatisfactory ([Okamoto 1968](#)) and questionable in another ([Elia 1966](#)). [Mira 2003](#) used AAO-NHS guidelines to establish a diagnosis of only "probable or possible Ménière's disease". In addition, there is a risk of bias in two trials ([Burkin 1967](#); [Ricci 1987](#)) through lack of clarity on the randomisation method and the absence of any recording of attrition. While the quality of outcome measures was good in two of these trials ([Ricci 1987](#); [Salami 1984](#)) it was moderate ([Elia 1966](#); [Mira 2003](#); [Okamoto 1968](#)) or poor ([Burkin 1967](#)) in the others. All outcomes were short-term except in the trial by [Ricci 1987](#).

In summary there is insufficient good evidence on the effect of betahistine on vertigo, hearing loss, tinnitus or aural fullness in clearly defined Ménière's disease. It has been suggested that betahistine may have a beneficial effect on patients with imbalance due to a variety of causes, not simply well-defined Ménière's. Moreover, by excluding studies in this review because of the poor diagnostic criteria used, a true positive effect of betahistine on patients with ill-defined 'dizzy' symptoms may have been missed. That is, the results may have given a 'false negative' conclusion. This is discussed further below under '[Implications for research](#)'.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that betahistine is effective or ineffective in patients with Ménière's disease or syndrome. It appears to be well tolerated.

Implications for research

A large randomised clinical trial is required to establish the efficacy of betahistine in Ménière's disease or syndrome. Although neither universally accepted nor ideally designed for drug trials, the AAO-HNS guidelines provide a standardised protocol for diagnosis and assessment that would form an ideal basis for future trials of betahistine.

A further systematic review will be undertaken to evaluate the effect of betahistine in patients with balance disturbance due to any cause. This will address a pragmatic question pertinent in particular to the primary care setting. That is, is betahistine useful in improving the well being of any 'dizzy' patient?

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Prof A Salami ([Salami 1984](#))

Mr T Wilmot FRCS ([Wilmot 1976](#))

Dr Y Hayakawa ([Okamoto 1968](#))

The following manufacturers kindly replied to requests for information on published and unpublished work:

Eisai Co Ltd (via Dr Y Hayakawa of Clinical Research Centre of Japan, Tokyo)

Rhone-Poulenc Rorer Australia Pty Ltd

Solvay Pharmaceuticals (Medical Information Unit, England and International Marketing, Germany)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Burkin 1967
Study characteristics

Methods	Double-blind, cross-over trial Two-week intervals Data extractable
Participants	22 patients with Ménière's disease (grade III)
Interventions	Betahistine 4 mg 4 times daily versus placebo
Outcomes	Vertigo (grade III). Dizziness reduced with betahistine
Notes	Allocation bias: medium Attrition bias: medium

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Elia 1966
Study characteristics

Methods	Double-blind, cross-over trial Two-week intervals Data extractable
Participants	18 patients with Ménière's disease (grade III)
Interventions	Betahistine 4 mg 4 times daily versus placebo
Outcomes	Vertigo (grade II). Reduced with betahistine

Betahistine for Ménière's disease or syndrome (Review)

Elia 1966 (Continued)

Tinnitus (grade I). Reduced with betahistine

Notes Allocation bias: low
Attrition bias: medium

Risk of bias

Bias	Authors' judgement	Support for judgement
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Allocation concealment (selection bias)	Low risk	A - Adequate
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Mira 2003

Study characteristics

Methods Randomised, double-blind, parallel trial

Participants 144 patients (81 Ménière's disease, 63 BPPV)
41 Ménière's patients allocated to betahistine group, 40 to placebo

Interventions Betahistine dihydrochloride 16 mg twice daily versus placebo (identical in colour, weight and flavour)

Outcomes Vertigo (grade I). Reduced with betahistine
Quality of life (grade III). Improved activity levels at 2 and 3 months with betahistine

Notes Allocation bias: low
Attrition bias: medium

Risk of bias

Bias	Authors' judgement	Support for judgement
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Allocation concealment (selection bias)	Low risk	A - Adequate
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Okamoto 1968

Study characteristics

Methods Double-blind, parallel trial
Two-week duration

Participants 36 patients with Ménière's disease (grade III, but very lax criteria)

Interventions Betahistine 18 mg twice daily versus placebo

Outcomes Vertigo (grade II). No difference from placebo
Hearing loss (grade II). No difference from placebo

Okamoto 1968 *(Continued)*

Tinnitus (grade I). Reduced with betahistine

 Notes Allocation bias: low
 Attrition bias: medium

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Ricci 1987
Study characteristics

Methods	Double-blind, parallel trial 30 to 40-week duration
Participants	10 patients with Ménière's disease (grade III)
Interventions	Betahistine 8 mg 3 times daily versus placebo
Outcomes	Vertigo (grade I). Reduced with betahistine Hearing loss (grade I). No difference from placebo Tinnitus (grade I). No difference from placebo Aural fullness (grade I). No difference from placebo
Notes	Allocation bias: medium Attrition bias: medium

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Salami 1984
Study characteristics

Methods	Double-blind, parallel trial 8-week duration
Participants	30 patients with Ménière's disease (grade III)
Interventions	Betahistine 8 mg 3 times daily versus placebo
Outcomes	Vertigo (grade I). Reduced with betahistine

Betahistine for Ménière's disease or syndrome (Review)

Salami 1984 *(Continued)*

Hearing loss (grade I). No difference from placebo
 Tinnitus (grade I). Reduced with betahistine
 Aural fullness (grade I). Reduced with betahistine

Notes Allocation bias: medium
 Attrition bias: low

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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Schmidt 1992
Study characteristics

Methods Double-blind, cross-over trial
 16-week intervals
 Data extractable

Participants 35 patients with Ménière's disease (grade II)

Interventions Betahistine 24 mg 3 times daily versus placebo

Outcomes Vertigo (grade III). Imbalance reduced equally by betahistine and placebo
 Hearing loss (grade I). No difference from placebo
 Tinnitus (grade I). No difference from placebo
 Aural fullness (grade I). No difference from placebo

Notes Allocation bias: medium
 Attrition bias: low

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Allocation concealment (selection bias)	Unclear risk	B - Unclear
---	--------------	-------------

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Canty 1981	Participants: included patients with and without Ménière's disease; data on Ménière's patients not extractable

Study	Reason for exclusion
Conraux 1988	Participants: included patients with and without Ménière's disease; data on Ménière's patients not extractable
Fischer 1985	Participants: included patients with and without Ménière's disease; data on Ménière's patients not extractable
Frew 1976	Intervention: cross-over trial; data not extractable
Hicks 1967	Allocation: not randomised
Legent 1988	Participants: included patients with and without Ménière's disease; data on Ménière's patients not extractable
Meyer 1985	Intervention: cross-over trial; data not extractable
Oosterveld 1984	Intervention: cross-over trial; data not extractable
Oosterveld 1989	Participants: Included patients with and without Ménière's disease; data on Ménière's patients not extractable
Redon 2010	Participants: all patients were post-surgical (had undergone vestibular neurectomy for disabling Ménière's disease and had confirmed vestibular areflexia)
Singarelli 1979	Participants: included patients with and without Ménière's disease; data on Ménière's patients not extractable
Solvay 2007	Participants: all patients were post-surgical (had undergone vestibular neurectomy for disabling Ménière's disease and had confirmed vestibular areflexia)
Watanabe 1967	Intervention: cross-over trial; data not extractable
Wilmot 1976	Intervention: cross-over trial; data not extractable
Wolfson 1967	Trial design: trial not double-blind

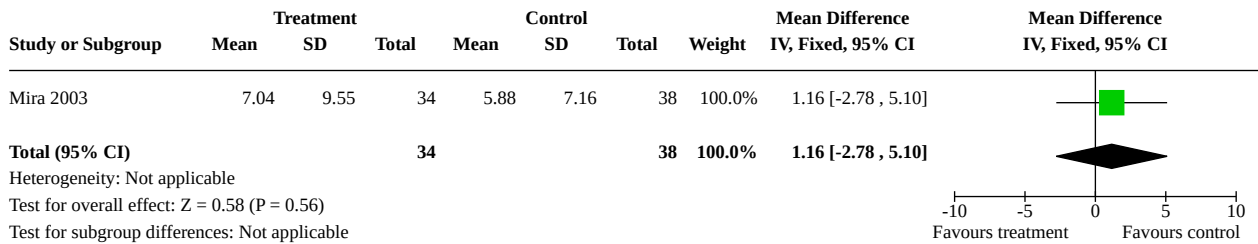
DATA AND ANALYSES

Comparison 1. Betahistine versus placebo - number of vertigo attacks

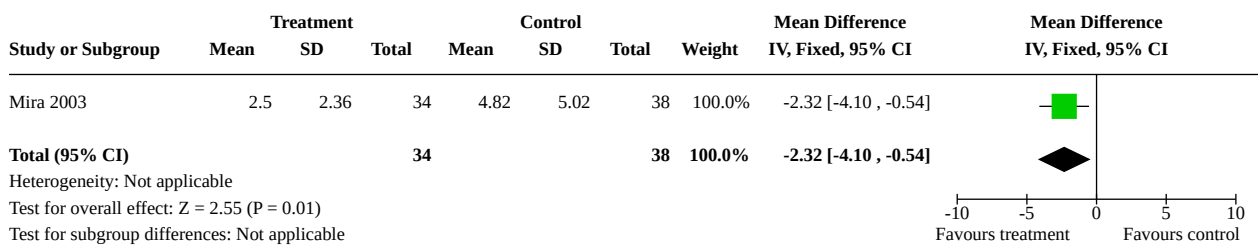
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Vertigo - number of attacks per month at baseline	1	72	Mean Difference (IV, Fixed, 95% CI)	1.16 [-2.78, 5.10]
1.2 Vertigo - number of attacks per month at 15 days	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.32 [-4.10, -0.54]
1.3 Vertigo - number of attacks per month at 1 month	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.37 [-3.94, -0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Vertigo - number of attacks per month at 2 months	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.27 [-4.40, -0.14]
1.5 Vertigo - number of attacks per month at 3 months	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.74 [-4.87, -0.61]

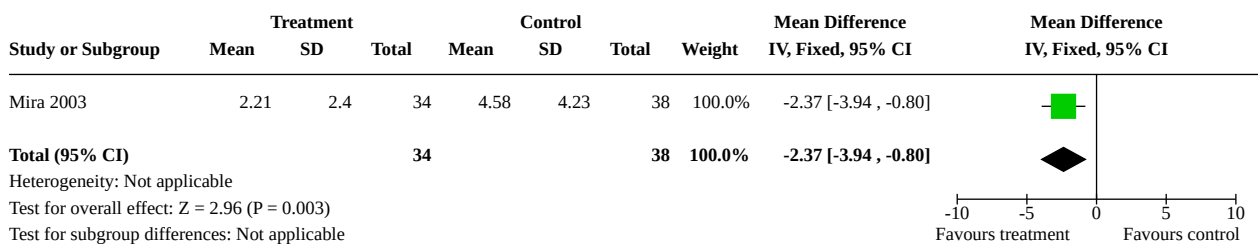
Analysis 1.1. Comparison 1: Betahistine versus placebo - number of vertigo attacks, Outcome 1: Vertigo - number of attacks per month at baseline



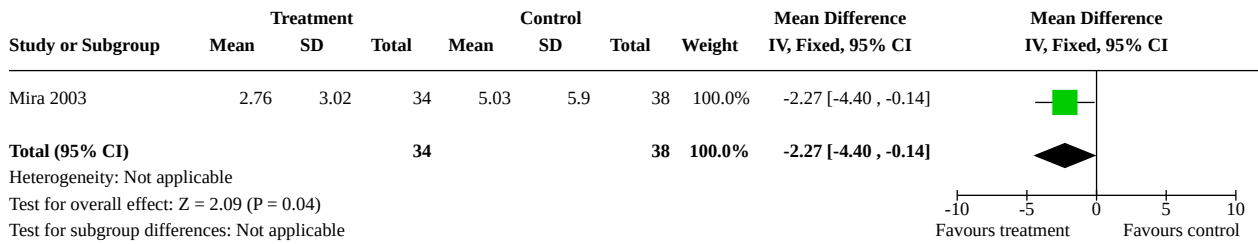
Analysis 1.2. Comparison 1: Betahistine versus placebo - number of vertigo attacks, Outcome 2: Vertigo - number of attacks per month at 15 days



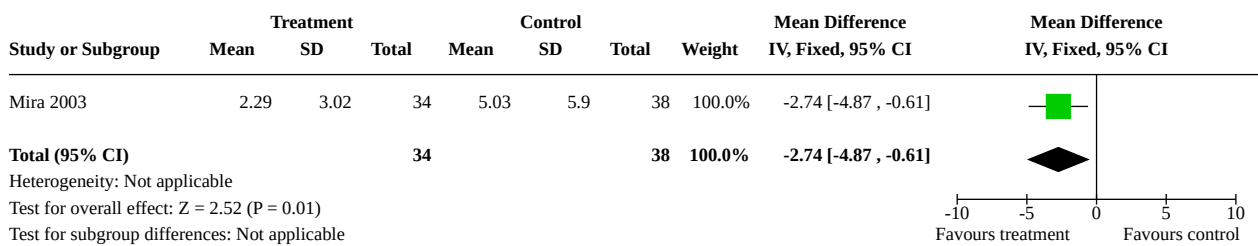
Analysis 1.3. Comparison 1: Betahistine versus placebo - number of vertigo attacks, Outcome 3: Vertigo - number of attacks per month at 1 month



Analysis 1.4. Comparison 1: Betahistine versus placebo - number of vertigo attacks, Outcome 4: Vertigo - number of attacks per month at 2 months



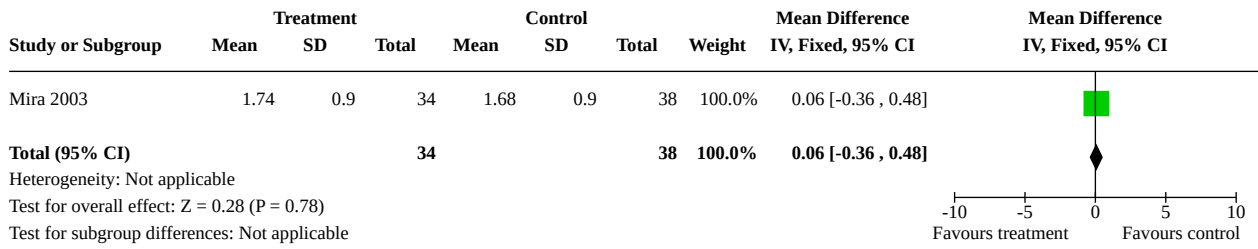
Analysis 1.5. Comparison 1: Betahistine versus placebo - number of vertigo attacks, Outcome 5: Vertigo - number of attacks per month at 3 months



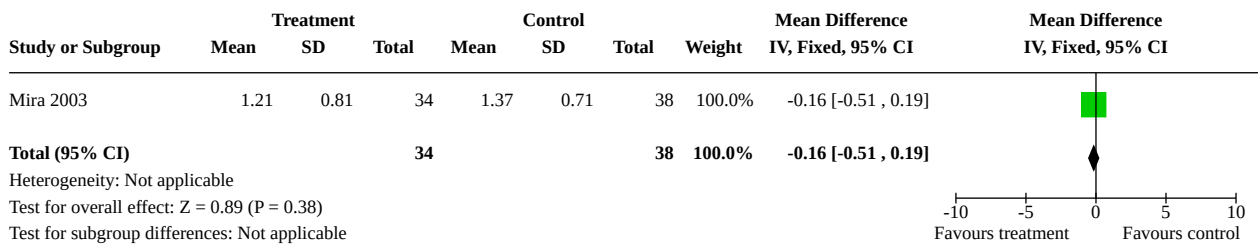
Comparison 2. Betahistine versus placebo - vertigo intensity scores

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Vertigo intensity scores at baseline	1	72	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.36, 0.48]
2.2 Vertigo intensity scores at 15 days	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.51, 0.19]
2.3 Vertigo intensity scores at 1 month	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.71, -0.01]
2.4 Vertigo intensity scores at 2 months	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.93, -0.13]
2.5 Vertigo intensity scores at 3 months	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.92, -0.18]

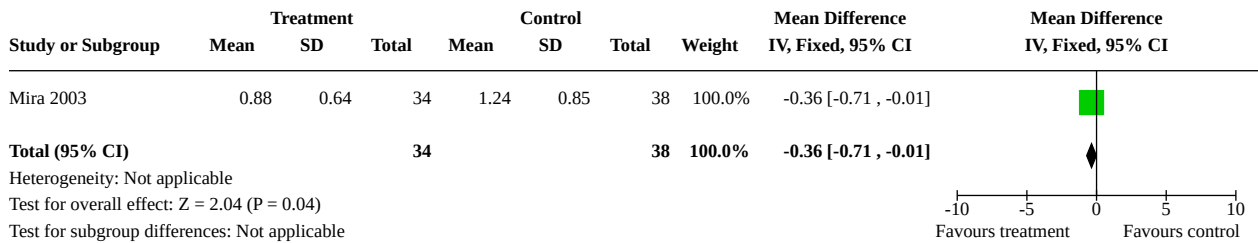
Analysis 2.1. Comparison 2: Betahistine versus placebo - vertigo intensity scores, Outcome 1: Vertigo intensity scores at baseline



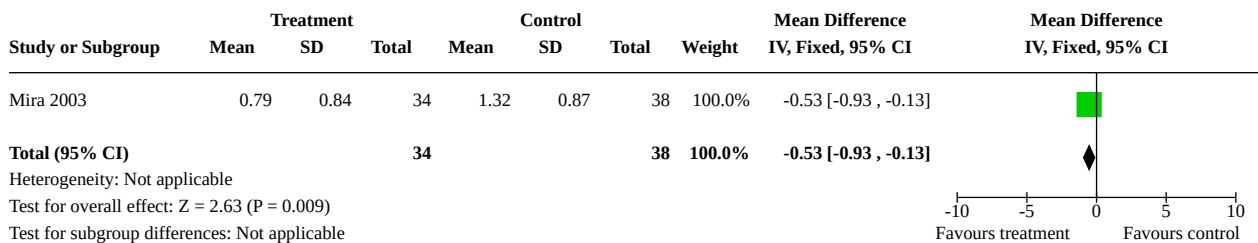
Analysis 2.2. Comparison 2: Betahistine versus placebo - vertigo intensity scores, Outcome 2: Vertigo intensity scores at 15 days



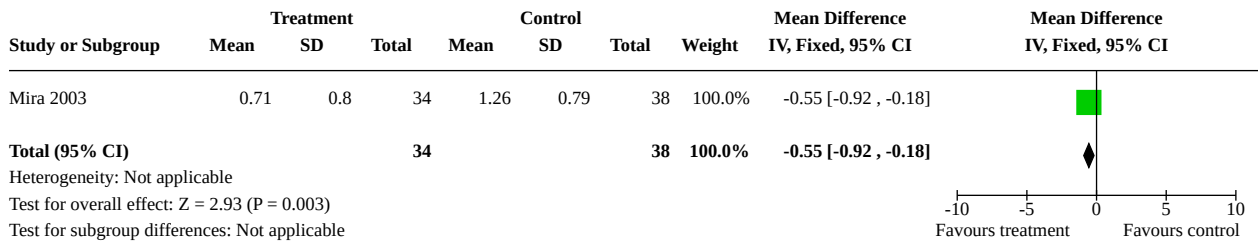
Analysis 2.3. Comparison 2: Betahistine versus placebo - vertigo intensity scores, Outcome 3: Vertigo intensity scores at 1 month



Analysis 2.4. Comparison 2: Betahistine versus placebo - vertigo intensity scores, Outcome 4: Vertigo intensity scores at 2 months



Analysis 2.5. Comparison 2: Betahistine versus placebo - vertigo intensity scores, Outcome 5: Vertigo intensity scores at 3 months



ADDITIONAL TABLES

Table 1. Quality of included studies

OVERALL GRADE	STUDY	YEAR	DIAGNOSTIC ACCURACY	OUTCOME QUALITY	RISK OF BIAS
A	None				
B	Schmidt	1992	II	I / III	Medium
C	Burkin	1967	III	III	Medium
C	Okamoto	1968	III	I / II	Low
C	Elia	1970	III	I / II	Low
C	Salami	1984	III	I	Medium
C	Ricci	1987	III	I	Medium
C	Mira	2003	III	II	Medium

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 MeSH descriptor Meniere Disease explode all trees	#9 #7 OR #8	1 MENIERE DISEASE/	S6 S4 and S5
#2 meniere*	#8 "Meniere Disease/drug therapy"[Mesh]	2 meniere*.tw.	S5 TX BETAHISTIN* or
#3 (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYN-DROME) or (aural and vertigo)	#7 #3 AND #6	3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYN-DROME) or (aural and ver-	BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or
	#6 #4 OR #5		
	#5 Betahistin* [tiab] OR BETAISTINA [tiab] OR SERC [tiab] OR AEQUAMEN		

Betahistine for Ménière's disease or syndrome (Review)

(Continued)

<p>or (labyrinth and vertigo) or (cochlea and hydrops) #4 (#1 OR #2 OR #3) #5 MeSH descriptor Betahistine explode all trees #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 #7 (#5 OR #6) #8 (#4 AND #7)</p>	<p>[tiab] OR BETASERC [tiab] OR BETASERK [tiab] OR BEATSERKA [tiab] OR EXTOVYL [tiab] OR FIDIUM [tiab] OR LECTIL [tiab] OR LOBIONE [tiab] OR MEGINALISK [tiab] OR MELOPAT [tiab] OR MENIACE [tiab] OR MERISLON [tiab] OR MICROSER [tiab] OR RIBRAIN [tiab] OR VASOMOTAL [tiab] #4 "Betahistine" [Mesh] #3 #1 OR #2 #2 meniere* [tiab] OR (ENDOLYMPHATIC [tiab] AND HYDROPS [tiab]) OR (LABYRINTH [tiab] AND HYDROPS [tiab]) OR (LABYRINTH [tiab] AND SYNDROME [tiab]) OR (aural [tiab] AND vertigo [tiab]) OR (labyrinth [tiab] AND vertigo [tiab]) OR (cochlea [tiab] AND hydrops [tiab]) #1 "ENDOLYMPHATIC HYDROPS" [Mesh]</p>	<p>tigo) or (labyrinth and vertigo) or (cochlea and hydrops).tw. 4 1 or 3 or 2 5 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).tw. 7 6 or 5 8 4 and 7 9 Meniere disease/dt [Drug Therapy] 10 8 or 9</p>	<p>LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL S4 S1 or S2 or S3 S3 TX (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops) S2 TX meniere* S1 (MH "Meniere's Disease")</p>
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Web of Science/ BIOSIS Previews (Web of Knowledge)	BIOSIS Previews (Ovid)	Cochrane Ear Nose and Throat Trials Register (ProCite)	ICTRP
<p>#3 #1 AND #2 #2 TS=(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) #1 TS=(meniere* OR (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops))</p>	<p>1 meniere*.tw. 2 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).tw.869 3 1 or 2 4 (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).tw. 5 3 AND 4</p>	<p>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</p>	<p>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 RIBRAIN or VASOMOTAL</p>

Appendix 2. Manufacturers of betahistine contacted for further information

Company	Street	District	Town	Post / Zip Code	Country	Brand Name	Reply
Solvay Healthcare	Gaters Hill	West End	Southampton	SO3 3JD	UK	Serc	Yes
Duphar	Avda Diagonal 507-9	08029 Barcelona			Spain	Serc	
Solvay Pharmaceuticals	Hans-Bockler-Allee 20	Postfach:220	30002 Han-nover		Germany	Serc / Be-taserc / Vaso-motal	Yes
Duphar (Ireland) Ltd	Ballymount Drive	Walkinstown	Dublin 12		Ireland	Serc	
Laboratories Duphar & Cie	60 Rue de Verdun	69625 Villeurbanne Cdx			France	Serc	
Promonta Lundbeck	Chemische Fabrik Promonta GmbH	Hammer Land-strasse 162-78	20537 Ham-burg		Germany	Aeqamen	
Kali Pharma GmbH	Donaustrasse 106	3400 Klosterneu-berg			Austria	Betaserc	
Solvay Pharma & Cie SNC	Boulevard Emile Bock-stael 122	1020 Brussels			Belgium	Betaserc	
Duphar Nedeland BV	Postbus 8198	1005 A M Weesp			Netherlands	Betaserc	
Kali Duphar Pharma AG	Postfach 6911	3001 Bern			Switzerland	Betaserc	
Marion Merrell Dow	130 Rue de Victor Hugo	BP 74	92303 Leval-lois- Perret Cdx		France	Extovyl	
Kabi Pharmacia	Ctra de Garcia-Manresa Km15	Sant Cugat del Valles	08090 Barcelona	Spain	Spain	Fidium	
Rhone Poulenc Rorer SA	Blvd Sylvian Dupuis 243	B3	1070 Brussels		Belgium	Lobione	
Medopharm Arzneimittelwerk	Dr Zillich GmbH & Co	Drosselgasse 5	Postfach:1380	82155 Grafelf-ing	Germany	Melopat	

(Continued)

Eisai Co Ltd	4-6-10 Koishikawa	Bunkyo-Ku	Tokyo 112-88		Japan	Merislon	Yes
Prodotti Formenti srl	Via Correggio 43	20149 Milan			Italy	Microser	
Yamanouchi Pharma GmbH	Im Breitspiel 19	69126 Heidelberg			Germany	Ribrain	
Fisons Pharmaceuticals	PO Box 191	Castle Hill	NSW 2154		Australia	Serc	Yes
Sanofi Winthrop	90 Allstate Parkway	Markham	Ontario	L3R 6H3	Canada	Serc	
Adcock Ingram Laboratories	Private Bag 1	Industria 2042			South Africa	Serc	

FEEDBACK

Comment received, July 2020

Summary

This review is very well performed. But, since 2016, at last, a very high quality RCT with 220 patients has been published: BEMED trial: Adrion et al, 2016 BMJ. Since 2016, I am waiting for the Cochrane review to be updated to include this extremely important RCT. Why has this not happened yet? Given that the BEMED trial has clearly shown the absence of any therapeutic effect of Betahistine, the obvious question arises: Is Cochrane getting money from the Betahistine industry? Why is Cochrane being biased by publication bias (or inclusion bias)??

Reply

Thank you for your comment. This review was last updated in 2010. The BEMED study referred to was therefore not complete when the review was published.

This review has not yet been updated because the Cochrane ENT editorial group is carefully [prioritising its work programme](#). Cochrane ENT is currently undertaking a formal 'scoping' and prioritisation exercise on the topic of [balance disorders](#). This aim of this project is to establish priority questions (including populations, interventions, comparators and outcomes) for new or updated systematic reviews on balance disorders. We expect work on the prioritised reviews to commence later this year (2020).

Ménière's disease is included in this project and if the use of betahistine is ranked as a priority question then a new, updated review will be conducted. If the study referred to meets the review inclusion criteria then its 'quality' will be formally assessed using the Cochrane 'Risk of bias' tool. The certainty of the evidence provided by the studies contributing to each presented outcome will be formally assessed and transparently reported using GRADE.

Cochrane takes the issue of conflict of interest very seriously and has a strict [policy](#) on this matter, which has been fully adhered to by all of the authors of this systematic review. None of the authors have any conflicts of interest in the conduct of the review, particularly in relation to the pharmaceutical manufacturer of betahistine.

Contributors

Comment: Gürkov R

Reply: Burton MJ, James A

WHAT'S NEW

Date	Event	Description
20 July 2020	Feedback has been incorporated	Comment and authors' reply incorporated.

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 1, 2001

Date	Event	Description
26 November 2010	New search has been performed	New searches run. We identified no new studies. One additional study was excluded (Redon 2010).
20 October 2008	Amended	Converted to new review format.
20 February 2008	New search has been performed	The review was updated following a new search (June 2007). One new included study (Mira 2003) and one new excluded study (Solvay 2007) were incorporated. No changes were made to the conclusions of the review.

CONTRIBUTIONS OF AUTHORS

Both authors independently selected studies, extracted data and assessed study quality. Both authors analysed the data and approved the final draft of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Betahistine [*therapeutic use]; Meniere Disease [*drug therapy]; Outcome Assessment, Health Care; Randomized Controlled Trials as Topic; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans