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Betahistine for symptoms of vertigo (Review)

Murdin L, Hussain K, Schilder AGM

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[Intervention Review]

Betahistine for symptoms of vertigo

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ABSTRACT

Background

Vertigo is a symptom in which individuals experience a false sensation of movement. This type of dizziness is thought to originate in the inner ear labyrinth or its neural connections. It is a commonly experienced symptom and can cause significant problems with carrying out normal activities. Betahistine is a drug that may work by improving blood flow to the inner ear. This review examines whether betahistine is more effective than a placebo at treating symptoms of vertigo from different causes.

Objectives

To assess the effects of betahistine in patients with symptoms of vertigo from different causes.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Trials Register; Central Register of Controlled Trials (CENTRAL 2015, Issue 8); PubMed; EMBASE; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. We also contacted manufacturers and researchers in the field. The date of the search was 21 September 2015.

Selection criteria

We included randomised controlled trials of betahistine versus placebo in patients of any age with vertigo from any neurotological diagnosis in any settings.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. Our primary outcome was the proportion of patients with reduction in vertigo symptoms (considering together the intensity, frequency and duration those symptoms).

Main results

We included 17 studies, with a total of 1025 participants; 12 studies were published (567 patients) and five were unpublished (458 patients). Sixteen studies including 953 people compared betahistine with placebo. All studies with analysable data lasted three months or less. The majority were at high risk of bias, but in some the risk of bias was unclear. One study, at high risk of bias, included 72 people with benign paroxysmal positional vertigo (BPPV) and compared betahistine with placebo; all patients also had particle repositioning manoeuvres. The studies varied considerably in terms of types of participants, their diagnoses, the dose of betahistine and the length of time it was taken for, the study methods and the way any improvement in vertigo symptoms was measured. Using the GRADE system,

we judged the quality of evidence overall to be low for two outcomes (proportion of patients with improvement and proportion with adverse events).

Pooled data showed that the proportion of patients reporting an overall reduction in their vertigo symptoms was higher in the group treated with betahistine than the placebo group: risk ratio (RR) 1.30, 95% confidence interval (CI) 1.05 to 1.60; 606 participants; 11 studies). This result should be interpreted with caution as the test for statistical heterogeneity as measured by the I^2 value was high.

Adverse effects (mostly gastrointestinal symptoms and headache) were common but medically serious events in the study were rare and isolated: there was no difference in the frequency of adverse effects between the betahistine and placebo groups, where the rates were 16% and 15% respectively (weighted values, RR 1.03, 95% CI 0.76 to 1.40; 819 participants; 12 studies).

Sixteen per cent of patients from both the betahistine and the placebo groups withdrew (dropped out) from the studies (RR 0.96, 95% CI 0.65 to 1.42; 481 participants; eight studies).

Three studies looked at objective vestibular function tests as an outcome; the numbers of participants were small, techniques of measurement very diverse and reporting details sparse, so analysis of this outcome was inconclusive.

We looked for information on generic quality of life and falls, but none of the studies reported on these outcomes.

Authors' conclusions

Low quality evidence suggests that in patients suffering from vertigo from different causes there may be a positive effect of betahistine in terms of reduction in vertigo symptoms. Betahistine is generally well tolerated with a low risk of adverse events. Future research into the management of vertigo symptoms needs to use more rigorous methodology and include outcomes that matter to patients and their families.

PLAIN LANGUAGE SUMMARY

Betahistine for symptoms of vertigo

Review question

Do patients suffering from vertigo from different causes benefit from the drug betahistine?

Background

Vertigo is a symptom in which individuals experience a false sensation of movement. This type of dizziness is thought to originate in the inner ear balance organ or its connections to the brain. It is a commonly experienced symptom and can cause significant problems with carrying out normal activities. Betahistine is a drug that may work by improving blood flow to the inner ear. This review examines whether betahistine is more effective than a placebo (sham medicine) at treating symptoms of vertigo from different causes in patients of any age.

Study characteristics

We included 17 studies, with a total of 1025 participants. Sixteen studies including 953 people compared betahistine with placebo; the studies were at high to unclear risk of bias. All studies with analysable data lasted three months or less. One study, at high risk of bias, included 72 people with benign paroxysmal positional vertigo (BPPV) and compared betahistine with placebo; all patients also had particle repositioning manoeuvres. We judged the quality of evidence overall to be low.

The studies varied considerably in terms of types of participants, their diagnoses, the dose of betahistine and the length of time the drug was taken for, the study methods and the way any improvement in vertigo symptoms was measured.

Key results

When all studies are taken together, the proportion of patients reporting a reduction of their vertigo symptoms was significantly higher in the betahistine group than in the placebo group. However, there was significant variability in the results of the studies so this result should be treated with caution.

The proportion of patients reporting side effects of the medication was similar in both groups: 16% in the betahistine groups and 15% in the placebo groups. Overall, 16% of patients of both groups withdrew from the studies.

There was insufficient information about the effect of betahistine on objective tests of inner ear balance organ function. There was no information on the effect of betahistine on overall quality of life or falls.

Quality of the evidence

We judged the quality of evidence from the included studies to be low, meaning our estimates of the effects of betahistine could turn out to be inaccurate. The evidence is up to date to September 2015.

Conclusion

Low quality evidence suggests that patients suffering from vertigo from different causes may have some benefit from betahistine in terms of reduction in vertigo symptoms. Betahistine is generally well tolerated. Future research into the management of vertigo symptoms needs to use more rigorous methodology and include outcomes that matter to patients and their families.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Betahistine versus placebo for symptoms of vertigo

Patient or population: patients with symptoms of vertigo
Setting: outpatient clinics
Intervention: betahistine
Comparison: placebo
Time frame: up to 3 months

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Quality of the evidence (GRADE)	What happens
		Without betahistine	With betahistine	Difference		
Benefits						
Proportion of patients with improvement according to global judgement of patient subgrouped by diagnosis № of participants: 606 (11 RCTs)	RR 1.30 (1.05 to 1.60)	Moderate			⊕⊕◯◯ LOW [123]	If 100 patients with vertigo are treated with betahistine, 60 will improve. This is 14 more than would have improved if a sham medicine had been taken instead of betahistine
		46.2%	60.1% (48.5 to 73.9)	13.9% more (2.3 more to 27.7 more)		
Harms						
Proportion of patients with adverse effects № of participants: 819 (12 RCTs)	RR 1.03 (0.76 to 1.40)	Moderate			⊕⊕◯◯ LOW [24]	If 100 patients with vertigo are treated with betahistine, 16 will experience adverse effects. This is 1 more than would have had similar symptoms if a sham medicine had been taken instead of

				betahistine
	15.2%	15.7% (11.6 to 21.3)	0.5% more (3.6 fewer to 6.1 more)	

*__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; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]Although statistical heterogeneity (I^2 statistic) was 64%, the direction of effects was consistent.
[2]Most evidence was from studies with serious methodological limitations (unclear sequence generation, allocation concealment and blinding).
[3]Non-validated outcome measures were used to measure improvement.
[4]Confidence intervals were wide and crossed thresholds of important benefits and harms.

BACKGROUND

Description of the condition

Dizziness is a term that is commonly used by patients to describe various sensations of lightheadedness, imbalance, illusory feelings of movement or disorientation. Unsurprisingly, perhaps, given its lack of specificity, the experience of dizziness is common. Four per cent of all patients registered with a GP in the UK suffer persistent symptoms of dizziness and at least 3% are severely incapacitated by their symptoms (Nazareth 1999).

Vertigo is a specific subtype of dizziness. It is defined by the Bárány Society (the international balance disorders association) as "the sensation of self-motion when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement" (Bisdorff 2009). It may be a sensation of rotation ('spinning vertigo'), or may be a different sensation of self motion ('non-spinning vertigo'). It is commonly, although not exclusively, caused by disease of the inner ear and can in this context be referred to as 'vestibular vertigo'.

In a large German epidemiological population-based study, the lifetime prevalence of vestibular vertigo was estimated at 7.4% (Neuhauser 2005). The same study found that the lifetime prevalence of vestibular vertigo requiring a medical consultation was 5.8%. Estimates of the prevalence of significant vertigo impacting on daily life range from 3% to 10% (Murdin 2015).

The pattern of symptoms of vertigo is variable. In some cases symptoms may be mild or there may be a single short-lived episode. Frequently, however, symptoms become prolonged or individuals become prone to recurrent attacks. The lifetime prevalence for recurrent attacks of vestibular vertigo is 6.5% (Neuhauser 2005). A Scottish study estimated that 21% of the population had experienced vertigo and 16% of these found the symptoms moderately or severely disruptive (Hannaford 2005). Importantly, vertigo increases the risk of falls, which in particular is becoming a major public health problem in the elderly.

Vertigo is a subjective experience. Its measurement is therefore dependent on the account of the individual experiencing it. There are some validated and well recognised instruments for assessing vertigo, for example the Dizziness Handicap Inventory (Jacobson 1990).

Vertigo has many causes including vestibular disorders such as Ménière's disease, vestibular neuritis, benign paroxysmal positional vertigo and migraine, each of which can be diagnosed by standardised criteria. Vestibular migraine is diagnosed according to criteria published jointly by the International Headache Society and the Bárány Society (Lempert 2012). Benign paroxysmal positional vertigo is diagnosed according to clinical criteria, as is vestibular neuritis (Strupp 2013). The Bárány Society and international collaborating organisations have recently published consensus clinical criteria for Ménière's disease (Lopez-Escamez 2015), taking forward the previously widely used American criteria (AAO-HNS 1995). Other causes of vertigo include neurological disorders affecting the central vestibular pathways (for example, some kinds of cerebellar stroke, or inflammatory or demyelinating pathologies) (Karatas 2010). Psychological disorders and primary cardiological disorders can also cause a sensation of vertigo (Newman-Toker 2008; Wiltink 2009). It is therefore important to assess patients presenting with vertigo very carefully to identify the underlying diagnosis. However, symptomatic management of vertigo may be required before a definitive cause can be identified.

Description of the intervention

Betahistine is a drug treatment, available only in oral form, usually taken in doses from 24 mg to 48 mg daily. It is excreted via the urinary system. It is also known as betahistine dihydrochloride and has a number of different proprietary names, including Serc, Betaserc and Hiserk. It has been used in some countries for many years as a treatment for Ménière's disease or syndrome, where it has been thought to be especially effective for the symptoms of vestibular vertigo. This widely held view was challenged by a Cochrane review that found no evidence of benefit in Ménière's disease or syndrome (James 2001). However, it has also been used more broadly for the treatment of vestibular vertigo. In a study of medical practice in a variety of settings across 13 countries worldwide betahistine was the most common drug prescribed, being issued in two-thirds of cases of vertigo. It was also the most common drug prescribed across every diagnostic group (Ménière's, benign paroxysmal positional vertigo, peripheral vestibular vertigo and 'other' vertigo) (Agus 2013). A German study set in primary care found that betahistine was prescribed in 6.6% of consultations for dizziness, and was most likely to be prescribed in 'unspecified dizziness', vestibular neuritis and benign paroxysmal positional vertigo (Kruschinski 2008).

The main adverse effects of betahistine relate to upper gastrointestinal tract symptoms; in general it is believed to be well tolerated.

How the intervention might work

Betahistine could act at either a peripheral (inner ear labyrinth) or central nervous sytem level, with current data favouring a predominantly peripheral mode of action.

Despite widespread use, the pharmacology of betahistine remains incompletely understood. Betahistine hydrochloride is a weak histamine H1 agonist and a strong H3 antagonist with virtually no H2 histamine receptor activity. Betahistine may act on the inner ear fluid mechanics by improving circulation in the cochlear stria vascularis (Ihler 2012; Martinez 1972), via an action on the precapillary sphincter with an associated reduction in excessive endolymphatic pressure, improving the function of vestibular hair cells.

Betahistine could also have effects on symptoms of vertigo via central nervous system activity. Betahistine can cross the blood-brain barrier: the cell bodies of histamine-containing neurons project throughout the brain, including the ventromedial hypothalamic nucleus, the thalamus and the cerebral cortex, and betahistine has measurable effects on regional cerebral blood flow (Barak 2008). Data from a single double-blind, placebo-controlled clinical study suggest significant effects of betahistine on some cognitive function tests (Pathy 1977). Another possible mechanism of action of betahistine is via inhibition of activity within the vestibular nuclei (Timmerman 1994).

Why it is important to do this review

Vertigo is a common symptom that has significant impact on the health and wellbeing of sufferers both at an individual and a population level. There are evidence-based treatments for common conditions that cause symptoms of vertigo (e.g. particle repositioning manoeuvres for benign paroxysmal positional vertigo (Hilton 2014; Hunt 2012); drug treatments for migraine (Linde 2004); rehabilitation for unilateral vestibular disorders like vestibular neuritis (McDonnell 2015)), and the first step in evaluating patients with this symptom should always be a proper assessment with a view to making a clear diagnosis to guide evidence-based management. However, there remains a need to evaluate other therapies for vertigo. This is because these treatments may be contraindicated in some patients and others may fail to respond or have ongoing symptoms. Importantly, many patients with vertigo do not meet clear-cut diagnostic criteria for a defined condition so disease-specific treatments cannot always be offered. In these cases betahistine is often prescribed in clinical practice.

Betahistine is a widely used treatment for Ménière's disease or syndrome. A Cochrane review showed that there is insufficient good evidence of an effect (James 2001). The authors suggested, however, that due to difficulties with adherence to the strict diagnostic criteria for Ménière's syndrome, a true positive effect of betahistine in patients with less well-defined symptoms may have been missed.

OBJECTIVES

To assess the effects of betahistine in patients with symptoms of vertigo from different causes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. We planned to include cross-over trials if the results from before the cross-over were extractable, to avoid the potential for carry-over effects.

Types of participants

Patients of any age with vertigo in community or other settings were eligible. Where patients were diagnosed with a specific vestibular condition, we noted the diagnostic criteria. We excluded those who had specific diagnoses of non-neurotological causes for vertigo (such as anxiety disorders or cardiac disease). We included all categories of neurotological diagnosis (including, for example, central neurological conditions and vestibular schwannoma).

Types of interventions

We considered any trial of betahistine versus placebo. Planned comparisons were:

- betahistine versus placebo;
- betahistine with an additional intervention versus placebo with an identical additional intervention.

We included all dose regimes and all formulations (e.g. slow-release preparations). We did not include comparisons with other drugs as their effects on vertigo have not been formally assessed. Concurrent use of other medication for non-neurotological conditions was acceptable if used equally in each group. Where an additional intervention was also used equally in both groups, we analysed this as a separate comparison.

Types of outcome measures

We examined outcomes as short-term (three months or under) and long-term (over three months).

The outcome measures below were not used as a basis for including or excluding studies.

Primary outcomes

- Proportion of patients with reduction in vertigo symptoms (considering together the intensity, frequency and duration those symptoms).
- Proportion of patients with adverse effects. Betahistine is thought to cause upper gastrointestinal adverse effects and we recorded these separately.

Secondary outcomes

- Proportion of participants withdrawing (dropping out) from the study due to all causes.
- Generic quality of life (we assessed disease-specific quality of life scales as part of the primary outcome).

- Vestibular function as tested with objective vestibular function tests: caloric tests, rotation tests, posturography and vestibular evoked myogenic potentials.
- Proportion of participants with falls, as a real-life indicator of overall functional balance.

Search methods for identification of studies

The Cochrane ENT 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 21 September 2015.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Trials Register (searched 21 September 2015);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 8);
- PubMed (1946 to 21 September 2015);
- Ovid EMBASE (1974 to 21 September 2015);
- Ovid CAB Abstracts (1910 to 21 September 2015);
- EBSCO CINAHL (1982 to 21 September 2015);
- Ovid AMED (1985 to 21 September 2015);
- LILACS, lilacs.bvsalud.org (searched 21 September 2015);
- KoreaMed (searched via Google Scholar 21 September 2015;
- IndMed, www.indmed.nic.in (searched 21 September 2015);
- PakMediNet, www.pakmedinet.com (searched 21 September 2015);
- Web of Knowledge, Web of Science (1945 to 21 September 2015);
- CNKI, www.cnki.com.cn (searched via Google Scholar 21 September 2015);
- ClinicalTrials.gov (searched via the Cochrane Register of Studies 21 September 2015);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (searched 21 September 2015);
- ISRCTN, www.isrctn.com (searched 21 September 2015);
- Google Scholar, scholar.google.co.uk (searched 21 September 2015);
- Google, www.google.com (searched 21 September 2015).

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 Cochrane 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 1.

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 PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

Two authors (LM and KH) independently scanned the initial search results to identify trials that appeared to meet the inclusion criteria. We used abstract review to eliminate any trials that were clearly ineligible. If either author identified a paper as potentially suitable, we reviewed the full text of the article. We resolved disagreements by discussion or with the input of the third author (AS).

Data extraction and management

Two authors (LM and KH) extracted data independently and synthesised the results. We used standardised data entry forms. There was no blinding of journal, author names or affiliations. With regard to subgroup analysis, we extracted data on underlying diagnosis if applicable, along with treatment protocol (dose and duration of drug).

For each study, we extracted information on study design, duration, randomisation, concealment, number of participants, setting of study, diagnostic criteria and exclusion criteria, age and sex distribution of participants, country of recruitment, co-morbidity, date of study, number of intervention groups, betahistine dose and duration, outcomes measured and definition of outcomes, missing data and final sample size, data on intensity, frequency and duration of vertigo, and data from other vertigo scales.

For the outcome proportion of patients with an improvement in symptoms, a variety of (non-validated) scales with different numbers of ordinal points were reported in the studies. Two different review authors independently dichotomised these into 'improved' or 'not improved' whenever possible.

When the required data were not available in the published accounts, we contacted the principal investigator to request the data.

Assessment of risk of bias in included studies

LM and KH undertook assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane 'Risk of bias' tool in RevMan 5 (RevMan 2014), which involves 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 in the first instance, with input from the third author (AS) if necessary.

Measures of treatment effect

The primary outcome measure of this review was the proportion of individuals with benefit from the drug, which is a dichotomous measure.
For binary (dichotomous) data we calculated the risk ratio (RR).
For intervention effect measures with continuous data we planned to calculate the difference in means (mean difference, MD) between the groups, provided that different studies used the same scale of measurement. We planned to calculate the standardised mean difference (SMD) if different scales were used.
For studies with ordinal data we checked, where possible, to see if the scale had been validated. Depending on the number points in these scales (and how the data were reported), we either dichotomised these or analysed them as continuous outcomes.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials allocate groups instead of individuals. The participants in each group may be related in some way, therefore this needs to be taken into account in the analysis, otherwise there is a unit of analysis error, which would produce an artificially small P value and a risk of false positive results. We planned to analyse these according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). However, we identified no cluster-randomised trials.

Cross-over trials

Cross-over trials may have a carry-over effect. We have included all patients with vertigo, some of which may resolve quite quickly. In view of this, and the chronic and episodic nature of the condition of interest (vertigo), we used data from cross-over trials only if data from before the cross-over could be obtained.

Multi-arm studies

Where 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 and relevant to each of the meta-analyses that we implemented. Where the study design used independent groups, we treated the study as an independent comparison.

Repeated observations on participants

In longer studies, results may be recorded at more than one time interval. In order to avoid a unit of analysis error when combining these results in a single meta-analysis (and therefore counting the same participants in more than one comparison), we would have defined different outcomes, based on different periods of follow-up, performing separate analyses.

Dealing with missing data

We did not plan or implement any statistical strategies to deal with missing data, except for imputations to estimate missing standard deviations according to the methods recommended in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We conducted available case analysis.

Assessment of heterogeneity

We assessed studies for clinical, statistical and methodological heterogeneity.
We assessed heterogeneity by inspection of the point estimates and confidence intervals on the forest plots. We assessed the variation in treatment effects by means of the Cochrane test for heterogeneity and quantified it using the I^2 statistic.
An approximate guide to interpretation provided in the *Cochrane Handbook for Systematic Reviews of Interventions* is as follows (Handbook 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We also used the Chi^2 test, using the indicator that where Chi^2 was greater than the degrees of freedom, heterogeneity was likely to be present. We considered heterogeneity statistically significant if the P value was < 0.1.

Assessment of reporting biases

Reporting bias can be assessed as *between-study publication bias* or *within-study reporting bias.*

Between-study publication bias

Where there was a sufficient number of trials (more than 10) in any meta-analysis, we assessed publication bias according to the recommendations on testing for funnel plot asymmetry as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Egger 1997; Handbook 2011).

Within-study reported bias

We planned to assess within-study reporting bias by comparing the outcomes reported in the published report against the outcomes reported in the study protocol, whenever this could be obtained. If a protocol could not be obtained, then we compared the outcomes listed in the methods section with those reported in the results.

Data synthesis

We planned to analyse all participants according to the group randomised in the studies. If the data were compatible and of sufficient quality we planned to combine them to give summary measures of effect. If sufficient data were available for different conditions (e.g. uncompensated vestibular disease), we planned to undertake subgroup analysis. As stated above, all conditions causing vestibular vertigo were to be included (including Ménière's disease), but at the subgroup analysis stage we did not plan to duplicate work already carried out on Ménière's disease since there is already a Cochrane review on this specific topic (James 2001).

Subgroup analysis and investigation of heterogeneity

We analysed subgroups by participant factors (diagnosis) and by intervention factors (dose of betahistine) to examine reasons for heterogeneity.

Sensitivity analysis

We planned to conduct a sensitivity analysis by comparing the effect of the inclusion and exclusion of studies based on eligibility criteria or data analysis methods where required.

GRADE and 'Summary of findings' table

We 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: 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 any estimate of effect obtained is very uncertain.

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, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We included the following outcomes in the 'Summary of findings' table:

- proportion of patients with improvement according to global judgement of patient subgrouped by diagnosis;
- proportion of patients with adverse effects.

RESULTS

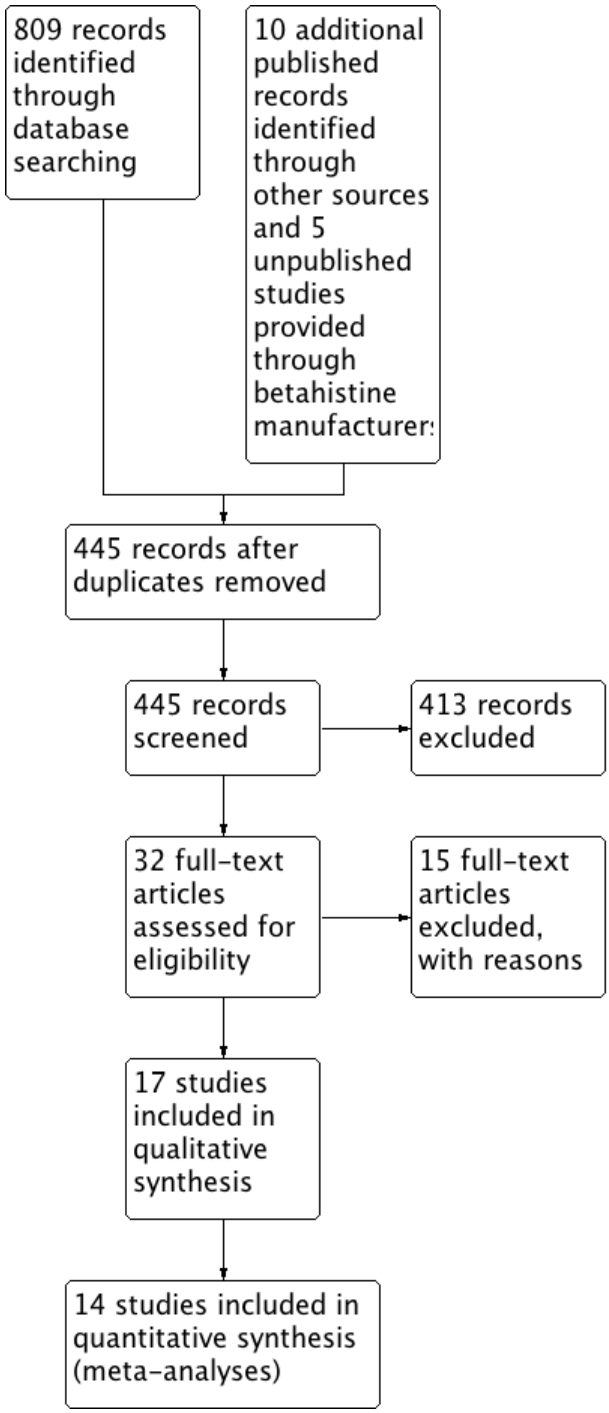
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The electronic database search on 21 September 2015 identified 809 records. We identified an additional 10 records from handsearching, contacting manufacturers and experts, and from the reference lists of relevant studies. We were provided with five further unpublished studies for analysis. After removal of duplicates we were left with 445 records. We identified 32 potentially eligible studies and excluded 15 for reasons including having a cross-over design with the data from before cross-over not extractable, lack of adequate randomisation and ineligible participants. Seventeen studies met the inclusion criteria. The results of the search are shown in Figure 1 as a flow chart. The excluded studies are tabulated in the Characteristics of excluded studies table. There are no studies awaiting assessment and two studies are ongoing.

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



Included studies

We included 17 studies and these are summarised in the Characteristics of included studiestable.

Only Guneri 2012 explicitly reported no financial conflict of interest. Six studies all acknowledge an association with the manufacturers of betahistine (Conraux 1988; Fischer 1985; Legent 1988; Mira 2003; Oosterveld 1989; Otto 2008), and five were unpublished industry studies (Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10802786F/M 1989; Duphar H10803592F 1997; Duphar H108906NL 1990).

Design

Most studies used a prospective, parallel-group comparison design (Conraux 1988; Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10802786F/M 1989; Duphar H10803592F 1997; Duphar H108906NL 1990; Fischer 1985; Guneri 2012; Legent 1988; Mira 2003; Okamoto 1968; Otto 2008; Ricci 1987; Salami 1984). Three studies used a cross-over design, from which data were extractable prior to cross-over (Burkin 1967; Canty 1981; Oosterveld 1989). In Guneri 2012, betahistine was compared to placebo for the treatment of benign paroxysmal positional vertigo (BPPV) in addition to usual care (the Epley particle repositioning manoeuvre). All studies were double-blinded.

Sample sizes

Sample size ranged from 10 (Ricci 1987) to 144 (Mira 2003). A total of 567 patients had results reported across the 12 published studies, and there were results for an additional 458 patients from the five unpublished studies (1025 patients in total).

Setting

The majority of studies were single-centre and appeared to take place in specialist centres. Mira 2003, Oosterveld 1989 and Legent 1988 were multicentre studies. Studies took place in the USA (Burkin 1967), the UK (Canty 1981), France (Conraux 1988; Legent 1988), the Netherlands (Fischer 1985; Oosterveld 1989), Italy (Mira 2003; Ricci 1987; Salami 1984), Turkey (Guneri 2012), Japan (Okamoto 1968), and Germany (Otto 2008). Of the unpublished studies, there were two multicentre studies from France (Duphar H10802786F/M 1989; Duphar H10803592F 1997), and one single-centre study each from the UK (Duphar 77054 1983), France (Duphar H10800580M 1984), and the Netherlands (Duphar H108906NL 1990).

Participants

Five studies included patients who were designated by the study authors as having clinically defined Ménière's disease or syndrome (Burkin 1967; Mira 2003; Okamoto 1968; Ricci 1987; Salami 1984). In only one of these were the AAO-HNS 1995 diagnostic criteria cited (Mira 2003), with participants having probable or possible Ménière's according to the study authors.

Three studies included patients with episodic vertigo (Canty 1981; Fischer 1985; Oosterveld 1989), and one included those with episodic vertigo "with or without cochlear symptoms suggestive of Meniere's disease" (Legent 1988). Canty 1981 specified that symptoms must have a presumed peripheral origin and to have lasted at least 12 months. Two studies included patients with BPPV defined by a positive Dix-Hallpike positioning test (Guneri 2012; Mira 2003). One study included patients with chronic vertigo (Conraux 1988), defined as at least six crises over the last two months and symptom duration of at least three months. One study included patients with "vertebrobasilar ischaemia", defined in this study as vertigo with at least two of impaired hearing, impaired vision, tinnitus or headache and "typical abnormalities" on test, which were not specified (Otto 2008).

Duphar 77054 1983, Duphar H10802786F/M 1989 and Duphar H10803592F 1997 included patients with Ménière's disease or episodic vertigo with cochlear symptoms, but with no strict diagnostic criteria and with other diagnoses included. Duphar H108906NL 1990 included patients with various diagnoses including a majority with BPPV and small numbers with other causes of episodic vertigo. Duphar H10800580M 1984 included patients labelled as having "central signs" with short-lived episodes of vertigo, this list including changes in handwriting, spontaneous or induced/gaze evoked nystagmus, nystagmus on cervical or vertebrobasilar privation test and unilateral or bilateral hypo- or hyperexcitability of vestibular function (Duphar H10803592F 1997).

Burkin 1967 did not report exclusion criteria. Canty 1981, Fischer 1985, Guneri 2012, Legent 1988, Mira 2003, Okamoto 1968, Oosterveld 1989, Otto 2008, Salami 1984 and Ricci 1987 did report exclusion criteria. Patients on other relevant vestibular medication were excluded by Conraux 1988, Fischer 1985, Guneri 2012, Otto 2008 and Salami 1984. No published studies excluded those who had previously been on betahistine, but two unpublished studies did (Duphar H10803592F 1997; Duphar H108906NL 1990).

All studies were of adults, but one study reported that the youngest participants were teenagers (Okamoto 1968). The oldest participants in the studies were in the eighth decade (Guneri 2012; Otto 2008). Two studies did not report age and gender data for participants (Conraux 1988; Legent 1988). Some studies had an upper age limit for inclusion (Fischer 1985; Mira 2003; Oosterveld 1989 used 65 years as the upper limit; Duphar H10800580M 1984;

Duphar H108906NL 1990; Duphar 77054 1983 used an upper limit of 70, Guneri 2012 used an upper limit of 79 years). All studies where gender was reported had mixed male and female participants.

Interventions

All studies compared betahistine against placebo.

Doses of betahistine ranged from daily totals of 16 mg (Burkin 1967), 24 mg (Ricci 1987; Salami 1984), 32 mg (Canty 1981; Mira 2003), 36 mg (Okamoto 1968; Otto 2008), or 48 mg (Fischer 1985; Legent 1988; Oosterveld 1989). The unpublished studies used totals of 36 mg (Duphar 77054 1983), or 48 mg (Duphar H10800580M 1984; Duphar H10802786F/M 1989; Duphar H10803592F 1997; Duphar H108906NL 1990). Some studies used variable doses (Conraux 1988). Duration of treatment available for analysis in this review was a fixed interval of two weeks (Burkin 1967; Guneri 2012; Okamoto 1968), one month (Duphar H10803592F 1997), five weeks (Oosterveld 1989), six weeks (Salami 1984), two months (Canty 1981; Duphar H108906NL 1990), and three months (Conraux 1988; Fischer 1985; Legent 1988; Mira 2003, Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10802786F/M 1989). Study duration was three months or less in all cases except Ricci 1987, where duration of therapy was variable (using a protocol of 10 times mean duration of interval between attacks for each patient to determine treatment length). In this small study of 10 patients therapy was for a mean of 10.4 months in the betahistine group and 7.0 months in the placebo group.

Guneri 2012 compared betahistine (48 mg daily) with placebo in patients with BPPV who had also received particle repositioning manoeuvres as an additional intervention.

Assessment of intervention integrity in the form of compliance was variably reported. Compliance checks were not reported in most studies (Burkin 1967; Conraux 1988; Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10802786F/M 1989; Guneri 2012; Legent 1988; Mira 2003; Ricci 1987; Salami 1984). Four studies made direct or indirect reference to compliance checks either by checking tablet containers or by labelling some patients as non-compliant (Canty 1981; Fischer 1985; Okamoto 1968; Oosterveld 1989). Three studies reported that compliance was explicitly checked by direct questioning and container checks (Duphar H10803592F 1997; Duphar H108906NL 1990; Otto 2008).

Outcomes

Proportion of patients with reduction in vertigo symptoms (considering together the intensity, frequency and duration those symptoms)

Ten studies collected data on patient global satisfaction with treatment using various different ordinal scales, which we interpreted as overall improvement where the rating was positive (Conraux 1988; Duphar H108906NL 1990; Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10803592F 1997; Fischer 1985; Legent 1988; Mira 2003; Oosterveld 1989; Otto 2008). In addition, four studies reported vertigo scores in a way that enabled us to quantify the proportion of patients who experienced overall improvement in vertigo symptoms, using either dichotomous or ordinal scales of overall benefit in terms of vertigo (Burkin 1967; Canty 1981; Conraux 1988; Okamoto 1968). These scales were not described as validated.

Seven studies collected parallel data on the investigator global impression of treatment (Fischer 1985; Duphar H108906NL 1990; Duphar 77054 1983; Duphar H10802786F/M 1989; Duphar H10800580M 1984; Duphar H10803592F 1997; Mira 2003). However, in this review we have focused on the more clinically relevant outcome of patient-reported improvement.

Guneri 2012 used published validated scales (Dizziness Handicap Inventory (Jacobson 1990), Vestibular Disorders Activities of Daily Living Scale (Cohen 2000), Vertigo Symptom Scale (Yardley 1998), and European Evaluation of Vertigo Scale (Megnigbeto 2001). Mira 2003 also used the Dizziness Handicap Inventory and some other scales whose validation references could not be obtained (Dizziness Assessment Rating Scale, GISFaV).

Ricci 1987 reported in narrative terms the small number of patients in that study. Burkin 1967 used a "dizzy or not" dichotomous outcome.

Intensity of vertigo

Okamoto 1968 used a three-point, author-defined ordinal scale to measure intensity of vertigo. Similarly, six studies used a four-point ordinal scale (Canty 1981; Duphar 77054 1983; Duphar H10803592F 1997; Fischer 1985; Otto 2008; Salami 1984), and six studies used a five-point ordinal scale (Conraux 1988; Duphar H10802786F/M 1989; Duphar H10800580M 1984; Duphar H10803592F 1997; Legent 1988; Oosterveld 1989). In Otto 2008, patients rated a number vertigo symptoms (unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, swaying, self motion triggered vertigo) and for each individual the mean score across all these symptoms was calculated.

Frequency of vertigo

Six studies reported the frequency of attacks (Duphar H108906NL 1990; Duphar H10803592F 1997; Fischer 1985; Legent 1988; Mira 2003; Oosterveld 1989). Duphar H10803592F 1997 reported the total number of attacks through the 30-day study period. Duphar H10802786F/M 1989 reported the time since the last attack at study endpoint.

Duration of vertigo

Two studies also reported duration of vertigo attacks on an author-defined four-point ordinal scale (Fischer 1985; Oosterveld 1989). Legent 1988 reported mean duration of attacks per patient in hours. Mean duration of attacks in seconds was recorded by two studies (Duphar H108906NL 1990; Duphar H108906NL 1990). Salami 1984 reported total duration of attacks.

Proportion of patients with adverse effects

All studies except Guneri 2012 and Ricci 1987 made some comment on tolerability or safety. Duphar H10802786F/M 1989 did not describe adverse effects directly but measured "tolerance" on a four-point ordinal scale.

Proportion of participants withdrawing (dropping out) from the study due to all causes

Withdrawal from study was reported clearly by six studies (Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10802786F/M 1989; Duphar H10803592F 1997; Mira 2003; Salami 1984).

Generic quality of life

No study included a general quality of life measure.

Vestibular function as tested with objective vestibular function tests

Three studies also reported vestibular function tests (caloric, stabilometry, nystagmography) (Canty 1981; Mira 2003; Salami 1984). Guneri 2012 and Mira 2003 used Dix-Hallpike positioning testing to assess resolution of BPPV. Although one study had a majority of participants with BPPV, Dix-Hallpike test outcomes are not reported (Duphar H108906NL 1990). Duphar 77054 1983 reported the intention to collect vestibulometric tests as outcomes, but these were not done at the "discretion of the investigator".

Proportion of participants with falls

No study reported on falls outcomes.

Excluded studies

See Characteristics of excluded studies for details of the 15 studies that we excluded. Five studies were of cross-over design, with data before cross-over not extractable (Frew 1976; Meyer 1985; Oosterveld 1984; Watanabe 1967; Wilmot 1976). We excluded six studies as there was no evidence of randomisation (Bertrand 1972; Hommes 1972; Purohit 1988; Singarelli 1979; Verspeelt 1996), or randomisation was inadequate (Elia 1966). We excluded two as the participants did not meet the criteria for the symptom definition of vertigo according to the review protocol (Redon 2011; Schmidt 1992).

Ongoing studies

Four registered clinical trials were identified through the search. Two studies were identified as progressing but with data not yet published. The co-ordinator of these two trials confirmed progress by personal communication (BEMED; BETAVEST). One registered clinical trial was a drug company trial of betahistine for post-vestibular neurotomy patients with Ménière's disease, which was closed in 2006 (NCT00160238). Another registered clinical trial entry (of betahistine for vertigo caused by cerebral infarction in posterior circulation) reported that the study was terminated early due to poor recruitment (NCT00474409). We contacted the registered companies for any results but these have not been received at the time of writing.

Risk of bias in included studies

Two authors (LM and KH) critically reviewed studies for risk of bias. We contacted lead study authors for further details of methodology where required. We also contacted authors for clarification of methodological issues where these were unclear. Prof Oosterveld replied to our enquiries to say that as the study took place such a long time ago, the original paperwork for the study is no longer available for inspection to clarify details or fill in missing data (Oosterveld 1989). No other responses had been received by the time of submission.

For sequence generation six studies had a low risk rating and 11 were unclear. For allocation concealment, two had a low risk rating and 15 were unclear. For blinding, three had a low risk rating, one had a high risk rating and 14 were unclear. For attrition bias, four were low risk and 10 were high risk. For reporting bias, nine were high risk and six low risk. In Canty 1981, some included participants in both groups had no symptoms at all throughout the whole trial duration, including the baseline assessment period, and this was also flagged up as a problem. Risk of bias is presented graphically 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.

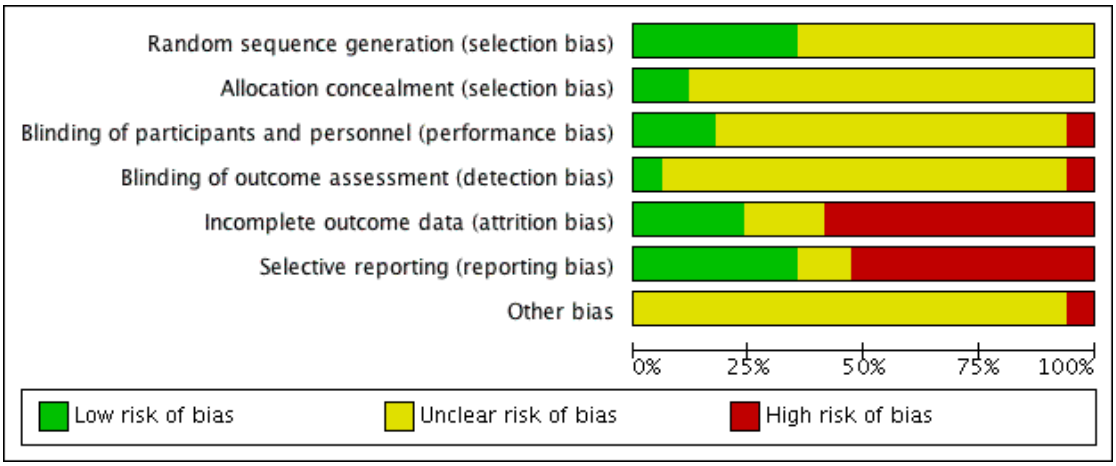
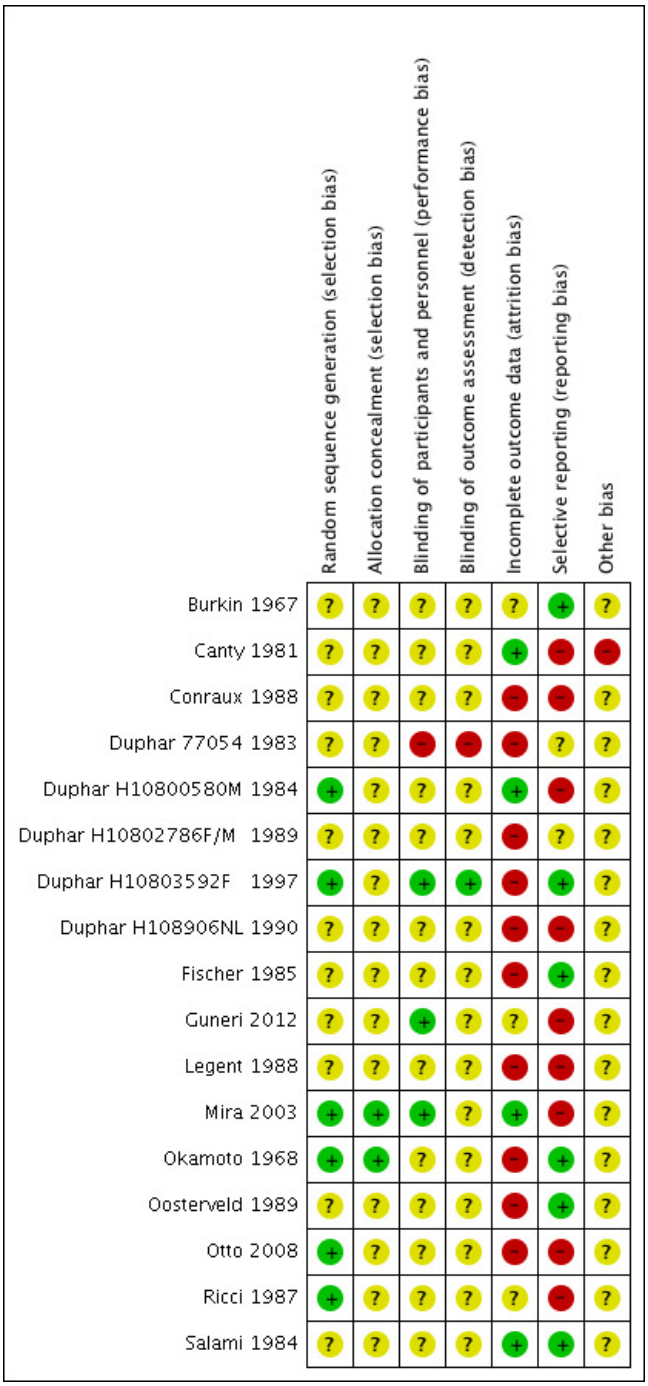


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

All studies reported that they were randomised. The majority (11 studies) gave no information on how this was achieved (Burkin 1967; Canty 1981; Conraux 1988; Duphar 77054 1983; Duphar H10802786F/M 1989; Duphar H108906NL 1990; Fischer 1985; Guneri 2012; Legent 1988; Oosterveld 1989; Salami 1984); the risk of bias was unclear. Six studies reported details of the randomisation methods, which were adequate and we considered them as at low risk of bias (Duphar H10800580M 1984; Duphar H10803592F 1997; Mira 2003; Okamoto 1968; Otto 2008; Ricci 1987).

Allocation concealment

Only Mira 2003 and Okamoto 1968 reported details relating to allocation concealment, with both reporting that the allocation was done on a different site to the investigating centre. These studies were at low risk of bias. All the other studies were at unclear risk of bias.

Blinding

All studies were reported as "double-blind" but most gave no further details, so we allocated these studies ratings of unclear risk. Primary outcome measures were mostly by self report, unsurprisingly, given the subjective nature of vertigo symptoms. Mira 2003 reported that drugs were supplied in identical packages with a false name, so we awarded it a low risk rating. Guneri 2012 commented on blinding of the trial physician and we also awarded this study a low risk rating on this basis. Most studies commented that the placebo tablet was "identical" or "indistinguishable" from the betahistine preparation, with only two giving no information (Guneri 2012; Ricci 1987). In Duphar 77054 1983, it is stated that envelopes were provided to all participants stating allocation, however returned sealed envelope collection is not reported and opacity was not stated, therefore we judged this high risk. Likewise, Duphar H10803592F 1997 stated "neither patient nor investigator knew which treatment was being given" and we allocated low risk. Duphar H10802786F/M 1989 described coding envelopes all being returned unopened, but opacity was not stated so we rated this as unclear.

Incomplete outcome data

Mira 2003 reported that randomised patients were all accounted for and there was a low rate of attrition so we rated it low risk. For Duphar H10800580M 1984, enough information was given for intention-to-treat (ITT) analysis to be possible and losses were under 20%. We judged it low risk on this item. Canty 1981 lost data on five of 32 participants, but reported data on all including one of the five who was subsequently found to be ineligible. However, the dropouts occurred in the second phase of cross-over, which is not relevant to the data considered for this review, so we deemed the study low risk.

Seven studies all reported some attrition but did not address this in the analysis or provide data that we could use to do so and so we rated them high risk (Duphar 77054 1983; Duphar H10802786F/M 1989; Duphar H108906NL 1990; Fischer 1985; Legent 1988; Oosterveld 1989; Otto 2008). For Duphar H10803592F 1997, information on all the lost participants was incomplete and we judged it high risk. Four studies did not give complete data for the group allocation of the lost participants (Conraux 1988; Fischer 1985; Legent 1988; Oosterveld 1989). Okamoto 1968 reported that two patients withdrew from each group, but not due to adverse effects (James 2001).

Salami 1984 reported zero attrition (personal communication reported in James 2001) and so we rated this low risk. Burkin 1967, Guneri 2012 and Ricci 1987 gave no information on attrition and we judged them unclear risk on this basis.

Selective reporting

No pre-published protocols were available for inspection to facilitate assessment for reporting bias. Conraux 1988 reported raw data and measures of spread were missing for important variables that were apparently collected, such as frequency of attacks; we thus rated it high risk. Guneri 2012 and Ricci 1987 did not report any information on adverse effects or tolerance and so we rated them high risk. Mira 2003 and Otto 2008 did not present absolute values or baseline data, only percentage changes in variables, so we rated them as high risk. Canty 1981 presented vertigo scores that are not fully described in the methods and we judged this high risk. Mira 2003 also recruited patients with benign paroxysmal positional vertigo but did not report Dix-Hallpike tests as an outcome. In Duphar H10800580M 1984, there were no data on neuro-otological findings although these were part of the diagnostic criteria and appear to have been assessed and so we judged this high risk. We rated the other studies unclear on the basis of the absence of a pre-published protocol.

Other potential sources of bias

Baseline similarity of groups with respect to clinical disease parameters, such as vertigo duration or severity, was not clearly reported in three studies (Burkin 1967; Conraux 1988; Guneri 2012). Four studies showed some differences between active and placebo

groups at baseline, not accounted for in the analysis techniques (Fischer 1985; Legent 1988; Otto 2008; Ricci 1987). Groups appear well matched in Okamoto 1968 and all the unpublished manufacturer trials (Duphar 77054 1983; Duphar H10800580M 1984; Duphar H10802786F/M 1989; Duphar H10803592F 1997; Duphar H108906NL 1990). Most studies did not exclude participants who had previously taken betahistine.

Effects of interventions

See: **Summary of findings for the main comparison** Betahistine versus placebo for symptoms of vertigo

Betahistine versus placebo

Primary outcomes

Proportion of patients with reduction in vertigo symptoms (considering together the intensity, frequency and duration of those symptoms)

The proportion of patients who reported overall reduction in symptoms is given in Analysis 1.1. Twelve studies yielded analysable data. Although Mira 2003 collected data using the validated Dizziness Handicap Inventory (DHI), the results were reported only as percentage reductions with no baseline absolute values and missing measures of spread, so no useful data could be extracted.

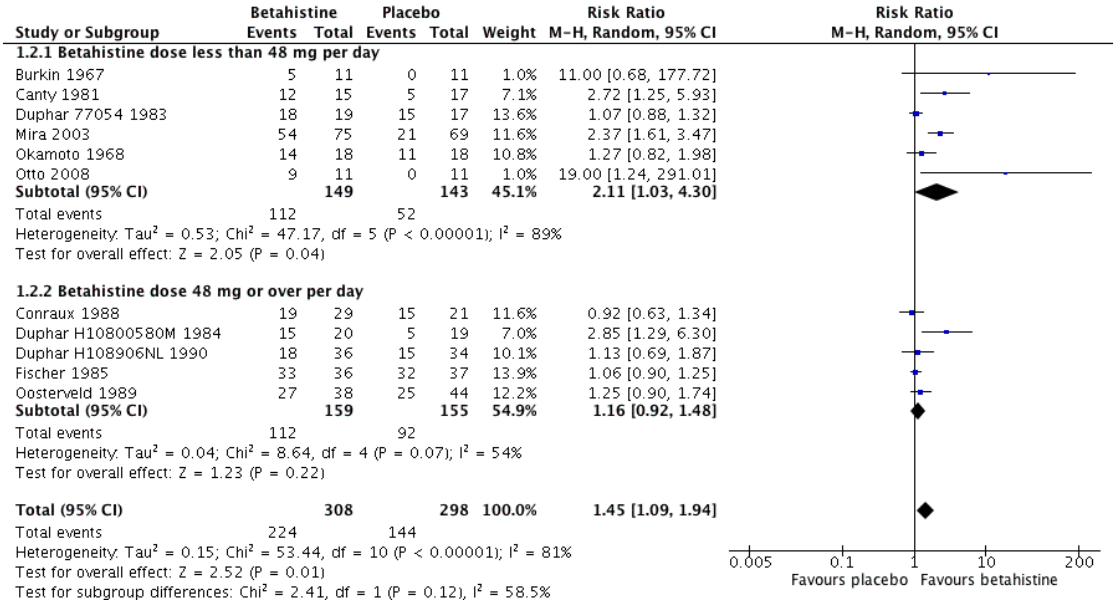
The pooled risk ratio (RR) was 1.30 (95% confidence interval (CI) 1.05 to 1.60; 606 participants; 11 studies, I^2 = 64%) in favour of betahistine. The heterogeneity was not resolved when we carried out subgroup analyses, first based on clinical diagnostic (participant) factors (Analysis 1.1), and then based on intervention factors (Analysis 1.2).

Firstly, in terms of clinical diagnostic (intervention) factors, we considered whether heterogeneity could be reduced by looking at the diagnostic groups of benign paroxysmal positional vertigo (BPPV), Ménière's disease (by investigator diagnosis) or 'other vertigo' (Analysis 1.1). These results need to be interpreted with caution as the diagnosis of Ménière's disease was investigator-defined and did not necessarily meet standard criteria.

Subgroups still showed high statistical heterogeneity (Ménière's: I^2 = 41%; other vertigo: I^2 = 68%). The pooled risk ratio for the Ménière's subgroup was 1.56 (95% CI 0.92 to 2.65; 139 participants; three studies), for BPPV it was 1.34 (95% CI 0.85 to 2.10; 63 participants; one study) and for 'other vertigo' it was 1.24 (95% CI 0.97 to 1.58; 404 participants; eight studies).

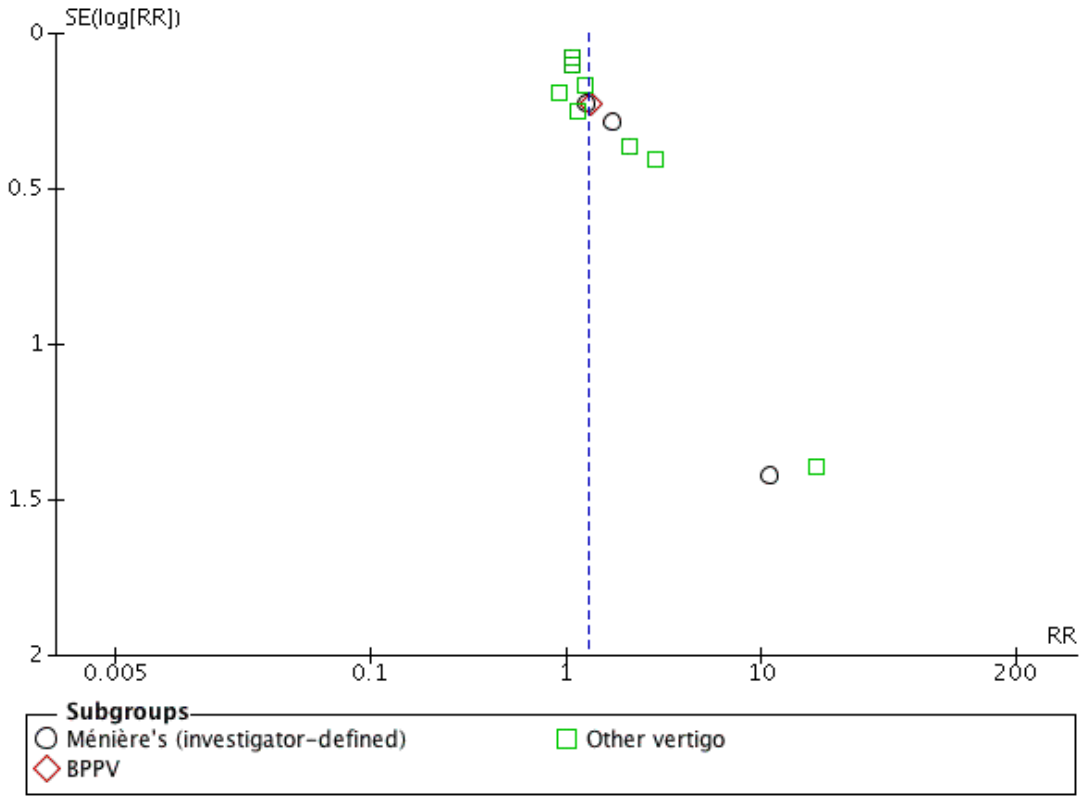
Secondly, in terms of intervention factors, we looked at total daily betahistine dosage (Analysis 1.2). For doses of betahistine under 48 mg per day, the pooled risk ratio was 2.11 (95% CI 1.03 to 4.30; 292 participants; six studies) in favour of betahistine, with the caveat that statistical heterogeneity was again high (I^2 = 89%). For higher doses (48 mg or more) the pooled RR was 1.16 (95% CI 0.92 to 1.48; 314 participants; five studies), also with high statistical heterogeneity (I^2 = 54%). This analysis is illustrated in Figure 4.

Figure 4. Forest plot of comparison: 1 Betahistine versus placebo, outcome: 1.2 Proportion of patients with improvement according to global judgement of patient: subgrouped by drug dose.



We created a funnel plot for this analysis, as more than 10 studies were included (Figure 5). We noted asymmetry, raising the possibility of publication bias. However, sensitivity analysis by removing two studies with low numbers of participants and large effect sizes, Burkin 1967 and Otto 2008, showed no difference in the overall effect size but reduced the statistical heterogeneity slightly (RR 1.23, 95% CI 1.04 to 1.45; 562 participants; 10 studies; I^2 = 49%) and the funnel plot was then symmetrical.

Figure 5. Funnel plot of comparison: 1 Betahistine versus placebo, outcome: 1.1 Proportion of patients with improvement according to global judgement of patient: subgrouped by diagnosis.



We rated the quality of the evidence for this outcome as low (see Summary of findings for the main comparison).

Proportion of patients with adverse effects

All trials except Ricci 1987 made reference to adverse effects. Among the other studies, there was marked variation in findings. The data for number of patients with adverse effects is shown in Analysis 1.3. The proportion of patients with adverse effects was 70/418 (16%) in the betahistine group and 61/401 in the placebo group (15%). Pooling the results give a risk ratio of 1.03 (95% CI 0.76 to 1.40; 819 participants; 12 studies).

Betahistine is frequently thought to cause upper gastrointestinal adverse effects. Six studies reported adverse effects in sufficient detail to analyse how many individuals reported upper gastrointestinal effects (Conraux 1988; Duphar 77054 1983; Duphar H10803592F 1997; Duphar H108906NL 1990; Mira 2003; Otto 2008). Studies that reported that no patients in either group had unwanted effects were not included in this analysis. Pooling the results for upper gastrointestinal effects gives a risk ratio of 1.38 (95% CI 0.67 to 2.82; 587 participants; six studies) (Analysis 1.4).

The next most common adverse effect reported in these studies was headache. Of those studies where headache was recorded as an unwanted effect in either group, the pooled risk ratio was 0.88 (95% CI 0.15 to 5.19; 515 participants; four studies) (Analysis 1.5).

Six studies reported no adverse events in either the placebo or betahistine groups (Burkin 1967; Canty 1981; Duphar H10800580M 1984; Fischer 1985; Okamoto 1968; Salami 1984). Legent 1988 reported non-vestibular complaint effects in 91% of both the placebo and the betahistine groups, but it was unclear how many patients were in each group. Oosterveld 1989 reported adverse effects in detail but this was a cross-over study and the figures provided pooled both cross-over periods so we did not include the data in this analysis. In Duphar H10802786F/M 1989, adverse events are reported as "tolerance" and given as "poor" in 0/21 in the betahistine group and 3/26 in the placebo group, so we did not include this study in the analysis for this outcome.

Adverse effects reported in the betahistine group included upper gastrointestinal symptoms, rash, weight gain, nausea, headache,

dry mouth, diuresis, rash, fatigue, tinnitus and hyperacusis. One patient in Mira 2003 was recorded as having dysmyelopoiesis on betahistine. One patient in Duphar H108906NL 1990 had respiratory distress on betahistine and one patient in Duphar H10803592F 1997 had an asthma attack on betahistine. No placebo patients reported these effects.
We rated the quality of the evidence for this outcome as low (see Summary of findings for the main comparison).

Secondary outcomes

Proportion of participants withdrawing (dropping out) from the study due to all causes

The proportion of participants who withdrew or were lost to follow-up is recorded in Analysis 1.6. We pooled the data, giving a risk ratio of 0.96 (95% CI 0.65 to 1.42; 481 participants; eight studies; I^2 = 0%).
There was no significant difference between the betahistine and placebo groups in any study or in the pooled analysis.

Generic quality of life

There were no studies that reported using a generic health-related quality of life instrument (e.g. SF-36). The Dizziness Handicap Inventory (DHI) is a mixture of quality of life and symptom severity scores, which is considered under symptom-specific measures.

Vestibular function as tested with objective vestibular function tests

Canty 1981, Salami 1984 and Otto 2008 included some objective measure of vestibular function.
Canty 1981 reported assessing caloric tests at baseline and after treatment, stating that the test was abnormal in nine patients before treatment with "some improvement" in two of these. As these effects were observed in a cross-over design study and details of the timing of drugs and tests were not given, we undertook no further interpretation for this review.
Craniocorpography results and evaluation for nystagmus are reported in Otto 2008. The paper reported a statistically significant difference in change in sway on Romberg and Unterberger tests, with a greater reduction in the betahistine group than in the placebo group.
Salami 1984 reported that in the betahistine group, in 13 patients with abnormal tests at baseline 10 patients (77%) had normalisation after six weeks of treatment. In the placebo group, 14 had abnormal tests at the beginning and this was unchanged at six weeks (0%). We calculate that this gives a P value of 0.006 (Fisher's exact test).
There was one study that included patients with benign paroxysmal positional vertigo and it did not report Dix-Hallpike tests as an outcome measure (Mira 2003).
Pooling data was inappropriate for this outcome given the diversity of techniques used to measure vestibular function.

Proportion of participants with falls

No studies reported falls as an outcome measure.

Betahistine plus particle repositioning versus placebo plus particle repositioning

Primary outcomes

Proportion of patients with reduction in vertigo symptoms (considering together the intensity, frequency and duration of those symptoms)

Guneri 2012 reported that there was no statistically significant difference ("P value > 0.05") in the mean scores between groups at one week. For the DHI, the authors reported that the placebo group had a mean score 12.15 (95% CI 10.5 to 13.4) at one week, and the betahistine group had a mean score of 10.42 (95% CI 4.7 to 16.1). On the Vertigo Symptom Scale (VSS) they reported that the placebo group had mean score of 2.88 (95% CI 2.83 to 2.93) at one week, and the betahistine group had a mean score of 2.17 (95% CI 2.13 to 2.21).

Secondary outcomes

Proportion of patients with adverse effects

Adverse effects were not reported.

Proportion of participants withdrawing (dropping out) from the study due to all causes

Withdrawals from the study were not reported.

Generic quality of life

Generic quality of life was not reported (although we note that the DHI has some symptom-specific quality of life aspects and this scale is considered above).

Vestibular function as tested with objective vestibular function tests

Guneri 2012 found persistently positive Dix-Hallpike tests (indicating no improvement) at one week in 4/26 (16%) with placebo and 3/24 (13%) with betahistine.

Proportion of participants with falls

Falls were not reported.

DISCUSSION

Summary of main results

The objective of this review was to evaluate the overall efficacy of betahistine for symptoms of vertigo.

The primary outcome of this review was the proportion of patients with overall clinical improvement. There was a pooled risk ratio for overall improvement of 1.30 (95% confidence interval (CI) 1.05 to 1.60) in favour of betahistine. The pooled data should be interpreted with caution as the tests of statistical heterogeneity gave high results. The evidence for the outcome "proportion of patients with reduction in vertigo symptoms" is of low quality using the GRADE assessment, especially with respect to blinding and randomisation, which are of huge importance when studying vertigo as an outcome measure.

The 17 studies in this review had 1025 participants. Of the 17 included studies, five were unpublished studies funded and led by the manufacturers of betahistine.

The studies took place over a maximum of three months and so the longer-term effects of betahistine are unknown.

Betahistine was associated with adverse events in 16% of participants; this was very similar to the rate in the placebo group (15%). The rate of upper gastrointestinal symptoms and headache was similar in the betahistine and placebo groups. There were two reports of asthma/respiratory distress in the betahistine group and none in the placebo group. There was one report of dysmyelopoiesis in the betahistine group and none in the placebo group. The high rate of unwanted symptoms in the placebo group was notable. This suggests that patients with vertigo may frequently experience other symptoms as part of their condition. However, the GRADE assessment for this outcome was also 'low', suggesting that the result should be interpreted with caution.

The review did not identify any subgroups that might particularly benefit from betahistine. This might be expected, given the fact that the studies were heterogeneous in terms of both participant diagnoses and also the diagnostic criteria used to identify subgroupings. Also, the overall effect size is at best a small one, meaning that numbers in any subgroup analysis are quite possibly too low to detect any effect. There is one pre-existing Cochrane review on betahistine for Ménière's disease or syndrome, which found no clear evidence of benefit in that group, and our findings are in keeping with this (James 2001).

The subgroup analysis did not indicate a dose response relationship of betahistine. When examining the effect of dose, there was evidence of a small effect in the studies using lower doses but not in the studies using higher doses. There could be a number of possible explanations for this observation. Firstly, it is possible that the effect in the low-dose group is a false positive finding. The GRADE quality of evidence for this outcome is low and the positive effect may be the result of study bias. Secondly, it is possible that the difference between the two subgroups is accounted for by other methodological differences between the studies, such as participant diagnoses. Thirdly, it is possible that the numbers of participants in the higher-dose group were inadequate to detect a small effect. It is important to remember that the absence of an effect in the higher-dose group in this subgroup analysis does not necessarily indicate that there genuinely is no effect. None of the included studies compared different doses of betahistine within the same protocol.

Overall completeness and applicability of evidence

The studies included in this review were conducted in clinical populations that appear to be similar to those who might receive betahistine in clinical practice, in that the participants all had vertigo with broad diagnostic inclusion criteria. However, they were all conducted using secondary or tertiary care level populations where there are more resources to make diagnoses. This means that there may be limited applicability to primary care settings where these resources are absent.

We searched a large number of databases and trial registries so we are confident that we traced all relevant trials. There is a concern, however, about potential reporting biases. We have overcome this as best we can by successfully obtaining unpublished evidence from manufacturers, sought by writing to manufacturers and from cited references in review papers. Of the 17 studies included, five were unpublished trials, but the manufacturers could provide us with data. We also found two registered clinical trials that had been terminated early due to poor recruitment (NCT00160238; NCT00474409). We contacted the drug companies sponsoring these trials, but no information had yet been provided to us at the time of publication of this review.

Quality of the evidence

Although we found a relatively large number of trials for this review (17 trials with 1025 participants), the overall quality of the evidence was low, meaning that further research is likely to have an

important impact on the interpretation of these results (Summary of findings for the main comparison).

There were significant methodological limitations in the conduct and reporting in these studies, particularly in terms of lack of clarity about patient recruitment/diagnostic criteria, choice of outcomes used (and reported) and very small sample sizes. None of the included studies used validated questionnaire data that could be analysed in this review.

None of the studies was of the highest methodological quality, with all studies except two rated as 'high risk' on at least one item of the 'Risk of bias' assessment. Statistical and clinical heterogeneity were high and few studies used validated outcomes, which are of critical importance for a subjective symptom such as vertigo. In addition, we are unsure about the quality of blinding of participants in the majority of studies. Although the studies were reported as "double blind", few details were supplied on how this was achieved. Since vertigo is a subjective outcome and is subject to psychological influences, adequate blinding is crucial in the execution of studies assessing the effects of interventions. However, with an intervention that is in tablet form, blinding should be straightforward to achieve.

None of the included studies had a pre-published protocol available for inspection. However, we note two ongoing or recently completed studies for which such a protocol is available (BEMED; BETAVEST).

Potential biases in the review process

Our searches of the electronic databases were comprehensive. Language was not a barrier to inclusion and we included papers in French, Italian, Japanese and Dutch. Author roles were pre-defined in the review process. Two authors selected studies for inclusion, extracted data and judged risk of bias independently, with recourse to the third author for resolution of disagreement or uncertainty. Two authors independently extracted data to minimise personal bias, and we considered both clinical and statistical heterogeneity before carrying out our analysis.

Agreements and disagreements with other studies or reviews

There are at least three other reviews of betahistine in the treatment of vertigo (Della Pepa 2006; Nauta 2014; Ramos 2015). Della Pepa 2006 and Nauta 2014 both found favourable effects of betahistine, as we did.

Nauta 2014 is a review and meta-analysis focused on the outcome "investigator global assessment of benefit". Nauta found a beneficial effect of betahistine over placebo for both Ménière's disease and vestibular vertigo, calculating a pooled odds ratio (OR) of 2.58 (95% CI 1.67 to 3.99), with sub-analyses conducted for patients with Ménière's disease (OR 3.37, 95% CI 2.14 to 5.29) and for vestibular vertigo (OR 2.23, 95% CI 1.20 to 4.14). Nauta did not consider risk of bias in underlying studies, nor other outcomes than investigator global opinion. For our review we chose to use the patient's perspective for improvement rather than the investigator's perspective.

Della Pepa 2006 is a review and meta-analysis of randomised controlled trials of betahistine against placebo for symptoms of vertigo carried out between 1979 and 2003. This analysis excluded studies of patients with Ménière's disease. Of the seven studies included (Canty 1981; Fischer 1985; Legent 1988; Mira 2003; Oosterveld 1989; Oosterveld 1984; Singarelli 1979), some are excluded from our review for methodological reasons (Oosterveld 1984; Singarelli 1979). The authors calculated an odds ratio in favour of betahistine of 3.52 (95% CI 2.40 to 3.51).

Ramos 2015 performed a narrative review without meta-analysis and concluded that betahistine is safe and effective.

Since we completed the search and analyses another relevant study has been published, which examines the effect of betahistine on vertigo in patients with Ménière's disease (Adrion 2016). This trial is noted in the ongoing studies section above (BEMED). The authors conclusions are that the incidence of attacks related to Ménière's disease did not differ between the three treatment groups and that treatment was well tolerated with no unexpected safety findings. This study will be included when this review is updated.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence that is largely of low quality suggests that in patients suffering from vertigo from different neuro-otological causes there may be a positive effect of betahistine in terms of reduction in vertigo symptoms. The same evidence suggests that betahistine is generally well tolerated with a similar risk of adverse events to placebo treatments.

Why might betahistine have an effect on such a heterogeneous group of patients with vertigo from so many different and contrasting conditions? One would have to hypothesise that the symptom of vertigo in a significant number of these individuals might have a common pharmacological basis located presumably in the labyrinth or brain or the connections thereof, and that betahistine is able to influence this favourably. However, the symptom of vertigo has many possible causes. The findings of this review do not negate the need for a proper clinical assessment of patients with the symptom of vertigo with the goal of making a diagnosis. There are many other evidence-based treatments for particular conditions that cause vertigo, which should be offered where appropriate.

This review and analysis were set up to answer the question, "is betahistine of overall benefit to patients with symptoms of vertigo? ". Patients and their doctors will want to know whether the overall

benefit from betahistine, if there is one, is large or small, and whether it is worth the risk of developing adverse effects. The review was not set up to analyse the size of any benefit since we examined only whether the patient judged that there was overall improvement of any degree, which makes it difficult for us to comment on how large the effect was. What we can say of the outcome measured was that patients overall felt there was benefit to them of taking the drug, taking all the relevant factors into consideration. We can also say that the number of patients who identified such a benefit over and above the placebo effect was small.

Implications for research

Future research into the effectiveness of betahistine in patients with vertigo should use rigorous methodology. There is a requirement for the development of and adherence to standardised diagnostic criteria for the selection of patients.

We also recommend the development of validated, patient-centred outcome measures for research in the field of balance disorders. At the time of the publication of this review, core outcome measures for dizziness had not been identified.

Randomisation and blinding should be of the highest quality, given the subjective nature of vertigo and the strong likelihood of a placebo response. Future studies should be conducted and reported according to the CONSORT statement. Recruitment of adequate numbers has clearly been problematic for researchers and this should be considered in future trial designs, such as by using a multi-centred trial design.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Burkin 1967

Methods	**Allocation:** randomised, but no further details given **Design:** cross-over with data extractable before cross-over occurred
Participants	**Number:** 22 analysed **Age:** 37 to 58 **Gender:** 50% female **Setting:** ENT department **Eligibility criteria:** investigator's clinical diagnosis of Ménière's disease **Exclusion criteria:** not specified **Baseline characteristics:** not given
Interventions	Betahistine 4 mg 4 times a day versus placebo over 2 weeks before cross-over **Intervention group:** n = 11 **Comparator group:** n = 11 **Use of additional interventions:** none
Outcomes	**Primary outcome:** dizziness - present or absent dichotomy **Secondary outcomes**: adverse events
Funding sources	Not specified
Declarations of interest	Not given
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; "neither patient nor investigator knew which group" but no further details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind

Burkin 1967 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information Participants lost to follow-up: not specified
Selective reporting (reporting bias)	Low risk	Appropriate outcomes
Other bias	Unclear risk	-

Canty 1981

Methods	**Allocation:** no information **Design:** cross-over with data extractable before cross-over occurred
Participants	**Number:** 32 randomised **Age:** 26 to 62 **Gender:** 29 M and 13 F **Setting:** not specified **Eligibility criteria:** episodic vertigo of peripheral origin for at least a year **Exclusion criteria:** central vertigo, Ménière's, asthma, peptic ulcer **Baseline characteristics:** no details
Interventions	Betahistine 32 mg for 8 weeks versus placebo **Intervention group:** n = 15 **Comparator group:** n = 17 **Use of additional interventions:** none
Outcomes	**Primary outcome:** vertigo scores (4-point ordinal scale) **Secondary outcomes:** caloric and oculomotor tests, adverse events
Funding sources	Not given
Declarations of interest	Not specified
Notes	Some participants in both groups had no symptoms throughout the trial duration

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind", but no further information

Canty 1981 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost to follow-up: 0 in first treatment phase (before cross-over)
Selective reporting (reporting bias)	High risk	Outcome measures unclear. Also using first arm of cross-over only. Adverse events only reported if "considered to represent adverse reactions to the study drug" without explicit criteria
Other bias	High risk	Some patients asymptomatic throughout entire trial period

Conraux 1988

Methods	**Allocation:** not reported **Design:** prospective, parallel comparison
Participants	**Number:** 57 randomised **Age:** not given **Gender:** not given **Setting:** multicentre **Eligibility criteria:** chronic vertigo for at least 3 months; 6 attacks in preceding 2 months **Exclusion criteria:** anti-vertigo drugs and other relevant medications **Baseline characteristics:** baseline group comparable for average intensity but otherwise baseline comparability unclear
Interventions	Betahistine up to 48 mg per day for 3 months versus placebo **Intervention group:** n = 27 **Comparator group:** n = 20 **Use of additional interventions:** none
Outcomes	**Primary outcome:** number of patients who improve with respect to vertigo symptoms **Secondary outcomes:** 5-point ordinal scale for intensity, patient and physician global assessment
Funding sources	Not given
Declarations of interest	1 co-author affiliated to manufacturer
Notes	"No difference" in adverse effects

Conraux 1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised", no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up: 10. Unclear which groups they belonged to. Analysis is "as treated"
Selective reporting (reporting bias)	High risk	Most outcomes not given as raw data or measures of spread missing
Other bias	Unclear risk	-

Duphar 77054 1983

Methods	**Allocation:** randomised, but no further detail **Design:** prospective, parallel-group, single centre
Participants	**Number:** 50 randomised **Age:** up to 70 **Gender:** 22 M, 14 F **Setting:** specialist centre **Eligibility criteria:** vertigo "likely to be of peripheral origin", "stable for 2 or 3 months" **Exclusion criteria:** other significant medical conditions (specified in report) **Baseline characteristics:** data provided in Table I and Table III of paper
Interventions	Betahistine 12 mg 3 times a day versus placebo for 12 weeks **Intervention group:** n = 19 **Comparator group:** n = 17 **Use of additional interventions:** none
Outcomes	**Primary outcome:** vertigo severity (4-point ordinal scale) **Secondary outcomes:** adverse effects

Duphar 77054 1983 (*Continued*)

Funding sources	Unpublished manufacturer data	
Declarations of interest	Unpublished manufacturer data	
Notes	Unpublished study	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised", no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Envelopes provided to participants stating allocation; returned sealed envelope collection not reported; opacity not stated
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Double blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	50 randomised, 33 analysed; betahistine participants dropped out due to increased symptoms or high anxiety levels making assessment difficult; analysis is "as treated" Participants lost to follow-up: 14
Selective reporting (reporting bias)	Unclear risk	No protocol available for inspection
Other bias	Unclear risk	No exclusion of participants who had previously taken betahistine

Duphar H10800580M 1984

Methods	**Allocation:** randomised, but not specified further **Design:** prospective, parallel-group, single centre
Participants	**Number:** 40 randomised **Age:** 20 to 70 **Gender:** 17 F 22 M **Setting:** ENT hospital department **Eligibility criteria:** vertigo attacks with "central signs" on ENG **Exclusion criteria:** some medications and neurological disorders **Baseline characteristics:** good similarity between groups for severity, duration of disease, duration of attacks (Table 3.7.1)

Duphar H10800580M 1984 (*Continued*)

Interventions	12 weeks betahistine 16 mg 3 times a day versus placebo **Intervention group:** n = 20 **Comparator group:** n = 20 **Use of additional interventions:** none
Outcomes	**Primary outcome:** intensity 5-point ordinal scale **Secondary outcomes:** patient and investigator global assessment
Funding sources	Unpublished manufacturer data
Declarations of interest	Unpublished manufacturer data
Notes	Unpublished study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation list drawn up before the start of the study outside treatment centre
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind. Coding envelopes all returned unopened. Opacity not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition and relatively complete datasets Participants lost to follow-up: 4
Selective reporting (reporting bias)	High risk	No data on neuro-otological signs though these were diagnostic criteria and appear to have been assessed
Other bias	Unclear risk	-

Duphar H10802786F/M 1989

Methods	**Allocation:** randomised, but no further details **Design:** prospective, parallel-group, multicentre (5 centres)
Participants	**Number:** 54 randomised, 38 analysed **Age:** mean 45.8 **Gender:** 20 M, 34 F **Setting:** 5 centres in France **Eligibility criteria:** at least 2 attacks of vertigo of over 2 minutes in the past 3 months at least 2 weeks apart; vertigo with and without cochlear symptoms **Exclusion criteria:** other causes of vertigo, relevant medications **Baseline characteristics:** comparable for age, sex, duration of history and time since last attack
Interventions	Betahistine 16 mg 3 times a day versus placebo for 90 days **Intervention group:** n = 27 **Comparator group:** n = 27 **Use of additional interventions:** none
Outcomes	**Primary outcome:** severity on 6-point ordinal scale (0 to 5) **Secondary outcomes:** frequency of attacks, severity of attacks, investigator global assessment
Funding sources	Manufacturer unpublished data
Declarations of interest	Manufacturer unpublished data
Notes	Unpublished study - manufacturer supplied data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in blocks of 4, but sequence generation method unclear
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up: 16. Analysis was "as treated"

Duphar H10802786F/M 1989 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Protocol not available for inspection
Other bias	Unclear risk	-

Duphar H10803592F 1997

Methods	**Allocation:** randomised in groups of 4 using tables before study started **Design:** prospective, parallel, multicentre
Participants	**Number:** 144 **Age:** 18 to 70 **Gender:** not specified but groups statistically equal **Setting:** French ENT specialist units **Eligibility criteria:** recurrent vertigo (at least 2 attacks, at least 1 in last month) including Ménière's disease and other **Exclusion criteria:** medical and psychiatric disorders (specified), vertigo due to other causes, contraindication to betahistine **Baseline characteristics:** Table 2 shows statistical assessment of similarity
Interventions	Betahistine 24 mg twice a day versus placebo for 30 days **Intervention group:** n = 119 **Comparator group:** n = 116 **Use of additional interventions:** none
Outcomes	**Primary outcome:** frequency, severity, duration of attacks **Secondary outcomes:** patient and investigator global assessment
Funding sources	Unpublished manufacturer study
Declarations of interest	Unpublished manufacturer study
Notes	Unpublished trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in groups of 4 before study started using tables
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes; opacity not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"neither patient nor investigator knew which treatment was being given"

Duphar H10803592F 1997 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up: 36. Reasons given for 28 of these
Selective reporting (reporting bias)	Low risk	Outcomes clearly reported
Other bias	Unclear risk	Previous trial with betahistine excluded

Duphar H108906NL 1990

Methods	**Allocation:** randomised, no further information **Design:** prospective, parallel-group, single centre
Participants	**Number:** 100 randomised **Age:** mean 56 (SD 12) in intervention group, mean 53 (SD 16) in placebo group **Gender:** 50 F, 24 M **Setting:** neurology department, Netherlands **Eligibility criteria:** vertigo 3 times a month or chronic **Exclusion criteria:** other specified medical conditions and medications. Previous trial with betahistine **Baseline characteristics:** data not given
Interventions	Betahistine 16 mg 3 times a day for 8 weeks **Intervention group:** n = 50 **Comparator group:** n = 50 **Use of additional interventions:** none
Outcomes	**Primary outcome:** duration of episodes in seconds, frequency of episodes per month **Secondary outcomes:** patient and investigator global opinion
Funding sources	Unpublished manufacturer data
Declarations of interest	Unpublished manufacturer data
Notes	Unpublished study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information

Duphar H108906NL 1990 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double blind"; no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind"; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	11 dropouts in betahistine group and 15 in placebo group; reasons unclear. Analysis was "as treated". Participants lost to follow-up: 26
Selective reporting (reporting bias)	High risk	Dropout data collected but not reported
Other bias	Unclear risk	-

Fischer 1985

Methods	**Allocation:** randomised, but no further information **Design:** parallel-group
Participants	**Number:** 83 randomised **Age:** 18 to 65 **Gender:** 43 F, 30 M **Setting:** Netherlands **Eligibility criteria:** episodic vertigo for at least 1 month prior to the beginning of the study and during this period for at least 2 episodes of dizziness **Exclusion criteria:** middle ear infections, cervical vertigo, head injury, cerebrovascular disease, epilepsy, Parkinson's, MS, pregnancy, patients on antihistamines, phenothiazines, vasodilators, barbiturates, tranquillisers **Baseline characteristics:** baseline disease duration longer in betahistine group
Interventions	Betahistine 16 mg 3 times a day versus placebo for 3 months **Intervention group:** n = 36 **Comparator group:** n = 37 **Use of additional interventions:** none
Outcomes	**Primary outcome:** vertigo intensity (4-point ordinal scale), frequency and duration of attacks **Secondary outcomes:** patient and physician global assessment
Funding sources	One co-author affiliated to manufacturer; statistical advice obtained from manufacturer

Fischer 1985 (*Continued*)

Declarations of interest	As for funding sources	
Notes	-	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	10 lost after randomisation and not included in analysis
Selective reporting (reporting bias)	Low risk	Appropriate outcomes reported
Other bias	Unclear risk	-

Guneri 2012

Methods	**Allocation:** randomised, but no further information **Design:** parallel-group
Participants	**Number:** 50 analysed **Age:** 18 to 79 **Gender:** 62.5% F, 37.5% M **Setting:** university hospital? **Eligibility criteria:** benign paroxysmal positional vertigo with positive Dix-Hallpike test **Exclusion criteria:** vestibulo-suppressant and ototoxic medications, central nervous system disorders and history of previous ear surgery **Baseline characteristics:** not stated
Interventions	Epley particle repositioning manoeuvre plus betahistine 24 mg twice a day versus Epley particle repositioning manoeuvre plus placebo over 2 weeks **Intervention group:** n = 24 **Comparator group:** n = 26

Guneri 2012 (*Continued*)

	Use of additional interventions: Epley repositioning manoeuvre used in both groups equally
Outcomes	**Primary outcome:** Dix-Hallpike positioning tests **Secondary outcomes:** Dizziness Handicap Inventory, Vertigo Symptom Scale, Vestibular Activities of Daily Living Scale, European Evaluation of Vertigo
Funding sources	Appropriate disclosures made
Declarations of interest	Appropriate disclosures made
Notes	Group 1 (Epley manoeuvre only) was discounted for this review as not relevant to review scope. Potential for bias due to additional intervention is noted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Physician doing Epley manoeuvre did not know who would be allocated." "... second physician who supplied medication was also unaware"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not mentioned Participants lost to follow-up: not reported
Selective reporting (reporting bias)	High risk	Adverse events not reported
Other bias	Unclear risk	-

Legent 1988

Methods	**Allocation:** randomised, but no further information **Design:** parallel-group
Participants	**Number:** 81 **Age:** not specified **Gender:** not specified **Setting:** ENT departments, France

Legent 1988 (*Continued*)

	Eligibility criteria: progressive episodic vertigo with or without cochlear symptoms **Exclusion criteria:** central vertigo, BPPV, tumours, CNS disease, iatrogenic, ear disease, pregnancy, psychiatric disease, asthma, gastrointestinal disease **Baseline characteristics:** betahistine group slightly lower intensity and longer duration of attack scores; raw data not given
Interventions	Betahistine 16 mg 3 times a day for 3 months versus placebo n = 59 in total in analysis, but unclear how many in each group (intervention/comparator) **Use of additional interventions:** none
Outcomes	**Primary outcome:** proportion of patients with "good results" **Secondary outcomes:** intensity (5-point scale), duration and frequency of attacks, global patient/doctor rating
Funding sources	One co-author affiliated to manufacturer
Declarations of interest	One co-author affiliated to manufacturer
Notes	Groups "similar at baseline" clinically but data not given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind; no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up: 22. Numbers lost in each treatment arm unclear
Selective reporting (reporting bias)	High risk	Raw data for outcomes missing, e.g. patient and investigator satisfaction
Other bias	Unclear risk	-

Mira 2003

Methods	**Allocation:** 2 randomised lists (one for MD and one for BPPV) generated by the pharmaceutical company that supplied the drug and placebo tablets, using Fisher and Yates random number tables **Design:** multicentre, parallel-group
Participants	**Number:** 144 randomised **Age:** range 18 to 65 **Gender:** (M:F) betahistine 33:42 placebo 27:42 **Setting:** 11 university hospitals **Eligibility criteria:** Ménière's disease (probable-possible, AAO-HNS (n = 81); benign paroxysmal positional vertigo (n = 63) **Exclusion criteria:** infections, cerebrovascular disease, drugs that act on cerebral circulation, antihistamines, calcium antagonists, anti-aggregants, thiazide diuretics, corticosteroids and benzodiazepines, having any major medical or surgical condition likely to interfere with the absorption, distribution, metabolism or excretion of the drug used in the study or having a terminal disease **Baseline characteristics:** percentages of patients who had used anti-vertigo drugs slightly higher in the betahistine group. Baseline data for dizziness scales not given
Interventions	Betahistine 16 mg twice a day for 3 months versus placebo **Intervention group:** n = 75 **Comparator group:** n = 69 **Use of additional interventions:** none
Outcomes	**Primary outcome:** number of vertigo attacks per month **Secondary outcomes:** Dizziness Handicap Inventory, GISFaV self rating scale, dizziness assessment rating scale, patient and physician global assessment, adverse events
Funding sources	Pharmaceutical company funded, interest declared
Declarations of interest	Pharmaceutical company funded, interest declared
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"according to the random list", "Randomisation in groups of 4". 2 randomised lists (one for MD and one for BPPV) generated by the pharmaceutical company that supplied the drug and placebo tablets, using Fisher and Yates random number tables
Allocation concealment (selection bias)	Low risk	As above

Mira 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"drugs supplied in identical packages with a fantasy name"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Randomised patients all accounted for; low rate of attrition Participants lost to follow-up: 8
Selective reporting (reporting bias)	High risk	Raw data frequently not given, only percentage change scores which are hard to interpret without baseline data. Dix-Hallpike test results not given as an outcome for patients with benign paroxysmal positional vertigo
Other bias	Unclear risk	-

Okamoto 1968

Methods	**Allocation:** random number allocation from a table by independent person not connected with the trial **Design:** parallel-group
Participants	**Number:** 40 randomised **Age:** teens to 70s **Gender:** 13 M, 23 F **Setting:** specialist unit, Japan **Eligibility criteria:** Ménière's disease (clinically defined) **Exclusion criteria:** vertigo due to other causes, e.g. central disorders **Baseline characteristics:** similar pre-trial symptom scores
Interventions	Betahistine 18 mg twice a day versus placebo over 2 weeks **Intervention group:** n = 18 **Comparator group:** n = 18 **Use of additional interventions:** none
Outcomes	**Primary outcome:** vertigo (3-point ordinal scale) **Secondary outcomes:** none
Funding sources	Not stated
Declarations of interest	Not stated

Okamoto 1968 (*Continued*)

Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number allocation from a table by independent person not connected with the trial (James 2001)
Allocation concealment (selection bias)	Low risk	Independently allocated identical bottles (James 2001)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	2 (out of 20 randomised) patients withdrew from each group, not due to adverse effects (James 2001) Participants lost to follow-up: 4
Selective reporting (reporting bias)	Low risk	Appropriate outcomes reported
Other bias	Unclear risk	-

Oosterveld 1989

Methods	**Allocation:** randomised, but no further information **Design:** cross-over with data extractable before cross-over
Participants	**Number:** 114 randomised **Age:** < 65 years old **Gender:** 46 F, 36 M **Setting:** 18 ENT practices in the Netherlands **Eligibility criteria:** episodic vertigo, at least 2 episodes of vertigo in the last month **Exclusion criteria:** vertigo secondary to middle/inner ear infection, Parkinson's, brain tumour, head trauma, epilepsy, multiple sclerosis or ocular diseases **Baseline characteristics:** baseline duration is longer in the placebo group
Interventions	Betahistine 16 mg 3 times a day for 10 weeks (5 weeks prior to cross-over) **Intervention group:** n = 38 analysed **Comparator group:**

Oosterveld 1989 (*Continued*)

	n = 44 analysed **Use of additional interventions:** none
Outcomes	**Primary outcome:** frequency, duration, severity of attacks (4-point scale) **Secondary outcomes:** global rating by patient, unwanted signs and symptoms
Funding sources	Not reported
Declarations of interest	Not reported. Pharmaceutical company assisted with preparation of report
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	32 missing/excluded; unclear from which groups some of them originate Participants lost to follow-up: 32
Selective reporting (reporting bias)	Low risk	Appropriate outcomes reported
Other bias	Unclear risk	-

Otto 2008

Methods	**Allocation:** computer-generated randomisation **Design:** parallel-group
Participants	26 with vertigo as part of "vertebrobasilar ischaemia" (see below, clinical diagnosis) **Number:** 26 randomised, 22 analysed **Age:** 31 to 70 **Gender:** (M:F) 7:19 **Setting:** ENT clinic, Germany **Eligibility criteria:** vertigo with at least 2 of impaired hearing, impaired vision, tinnitus,

	headache ("vertebrobasilar ischaemia" according to authors), 2 weeks off anti-vertigo drugs **Exclusion criteria:** other causes of vertigo, other medical conditions (specified) **Baseline characteristics:** baseline female predominance in placebo group
Interventions	Betahistine 12 mg 3 times a day versus placebo for 4 weeks **Intervention group:** n = 13 **Comparator group:** n = 13 **Use of additional interventions:** none, but study also included a third group treated with fixed combination of cinnarizine and dimenhydrinate, which was the main intervention of interest to the study authors
Outcomes	**Primary outcome:** vertigo scores (4-point scale) **Secondary outcomes:** overall efficacy rated by both patients and investigator on a 5-point scale
Funding sources	Not stated
Declarations of interest	1 co-author affiliated to manufacturer
Notes	Study was designed to compare betahistine and placebo with a third comparator group (fixed proprietary combination of dimenhydrinate and cinnarizine). Only the betahistine/placebo comparison is included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	High risk	15% lost to follow-up in each group Participants lost to follow-up: 4
Selective reporting (reporting bias)	High risk	Study was designed for a different purpose (assessment of the effect of a different drug)

Other bias	Unclear risk	-

Ricci 1987

Methods	**Allocation:** "randomisation list" **Design:** parallel-group
Participants	**Number:** 10 analysed **Age:** mean 36 **Gender:** 6 M, 4 F **Setting:** outpatients, Italy **Eligibility criteria:** Ménière's syndrome, investigator-defined **Exclusion criteria:** allergy to betahistine, ulcer, other medical conditions as defined **Baseline characteristics:** similar baseline characteristics
Interventions	Betahistine 8 mg 3 times a day versus placebo for variable duration (10 x mean duration of interval between attacks for each patient) **Intervention group:** n = 5 **Comparator group:** n = 5 **Use of additional interventions:** none
Outcomes	**Primary outcome:** narrative only (description of each patient's history) **Secondary outcomes:** none
Funding sources	Not stated
Declarations of interest	Not stated
Notes	**Participants lost to follow-up:** not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation list"
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information

Ricci 1987 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	High risk	Limited outcome data and no information on adverse events
Other bias	Unclear risk	-

Salami 1984

Methods	**Allocation:** randomised, but no further information **Design:** parallel-group
Participants	**Number:** 30 randomised **Age:** mean 46 (SD 4) **Gender:** 17 M, 13 F **Setting:** Italy **Eligibility criteria:** Ménière's disease, clinically defined **Exclusion criteria:** other causes of vertigo **Baseline characteristics:** groups similar at baseline
Interventions	Betahistine 8 mg 3 times a day versus placebo over 6 weeks **Intervention group:** n = 15 **Comparator group:** n = 15 **Use of additional interventions:** none
Outcomes	**Primary outcome:** vertigo intensity on a 4-point scale **Secondary outcomes:** vestibular function tests (electronystagmography and caloric testing)
Funding sources	Not stated
Declarations of interest	Not stated
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised"; no further information
Allocation concealment (selection bias)	Unclear risk	Method not stated

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition (James 2001)
Selective reporting (reporting bias)	Low risk	Outcomes and adverse events reported
Other bias	Unclear risk	-

AAO-HNS: American Academy of Otolaryngology - Head and Neck Surgery
BPPV: benign paroxysmal positional vertigo
CNS: central nervous system
ENG: electronystagmogram
ENT: ear, nose and throat
F: female
M: male
MD: Ménière's disease
MS: multiple sclerosis
SD: standard deviation

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

Study	Reason for exclusion
Bertrand 1972	ALLOCATION: No randomisation
Elia 1966	ALLOCATION: Quasi-randomised rather than truly randomised
Frew 1976	DESIGN: Cross-over with data not extractable
Hommes 1972	ALLOCATION: No randomisation
Meyer 1985	DESIGN: Cross-over with data not extractable

(*Continued*)

NCT00160238	Study terminated early, no data available
NCT00474409	Study terminated early, no data available
Oosterveld 1984	DESIGN: Cross-over with data not extractable
Purohit 1988	ALLOCATION: No randomisation
Redon 2011	ALLOCATION: Randomised controlled trial PARTICIPANTS: Participants do not meet inclusion criteria (symptoms of imbalance not vertigo)
Schmidt 1992	ALLOCATION: Randomised controlled trial PARTICIPANTS: Participants do not meet inclusion criteria (symptoms of imbalance not vertigo)
Singarelli 1979	ALLOCATION: No randomisation
Verspeelt 1996	ALLOCATION: No randomisation
Watanabe 1967	DESIGN: Cross-over with data not extractable
Wilmot 1976	DESIGN: Cross-over with data not extractable

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

BEMED

Trial name or title	'Medical treatment of Meniere's disease with betahistine: a placebo-controlled, dose-finding study'
Methods	Placebo-controlled, double-blind, randomised controlled trial
Participants	Ménière's disease
Interventions	1. Therapy with high-dose betahistine (3 x 48 mg) 2. Therapy with low-dose betahistine (2 x 24 mg) 3. Placebo

BEMED (*Continued*)

Outcomes	Number of vertigo attacks Median duration of vertigo attacks and median severity of vertigo attacks
Starting date	2007
Contact information	Prof M Strupp Klinikum Grosshadern Abt. f. Neurologie Marchioninistrasse 15
Notes	Recruitment completed. Data reportedly in analysis (Prof M Strupp, personal communication)

BETAVEST

Trial name or title	'Effects of betahistine on central vestibular compensation in acute unilateral vestibular failure: a double-blind, placebo-controlled trial'
Methods	Double-blind, placebo-controlled trial
Participants	Acute unilateral vestibular failure
Interventions	Betahistine 24 mg versus placebo
Outcomes	Time to recovery from acute symptoms
Starting date	2010
Contact information	Prof M Strupp Klinikum Grosshadern Abt. f. Neurologie Marchioninistrasse 15
Notes	Ongoing (Prof Strupp, personal communication)

DATA AND ANALYSES

Comparison 1. Betahistine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients with improvement according to global judgement of patient: subgrouped by diagnosis	11	606	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.05, 1.60]
1.1 Ménière's (investigator-defined)	3	139	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.92, 2.65]
1.2 BPPV	1	63	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.85, 2.10]
1.3 Other vertigo	8	404	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.97, 1.58]
2 Proportion of patients with improvement according to global judgement of patient: subgrouped by drug dose	11	606	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.09, 1.94]
2.1 Betahistine dose less than 48 mg per day	6	292	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.03, 4.30]
2.2 Betahistine dose 48 mg or over per day	5	314	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.92, 1.48]
3 Proportion of patients with adverse effects	12	819	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.76, 1.40]
4 Proportion of patients with upper gastrointestinal adverse effects	6	587	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.67, 2.82]
5 Proportion of patients with headache	4	515	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.15, 5.19]
6 Withdrawal from study	8	481	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.65, 1.42]

Analysis 1.1. Comparison 1 Betahistine versus placebo, Outcome 1 Proportion of patients with improvement according to global judgement of patient: subgrouped by diagnosis.

Review: Betahistine for symptoms of vertigo

Comparison: 1 Betahistine versus placebo

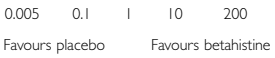
Outcome: 1 Proportion of patients with improvement according to global judgement of patient: subgrouped by diagnosis

Study or subgroup	Betahistine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Menière's (investigator-defined)					
Burkin 1967	5/11	0/11		0.5 %	11.00 [0.68, 177.72]
Mira 2003 (1)	21/41	12/40		7.7 %	1.71 [0.98, 2.99]
Okamoto 1968	14/18	11/18		9.6 %	1.27 [0.82, 1.98]
Subtotal (95% CI)	**70**	**69**		**17.8 %**	**1.56 [0.92, 2.65]**
Total events: 40 (Betahistine), 23 (Placebo)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 3.38$, df = 2 (P = 0.18); $I^2 = 41\%$					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 BPPV					
Mira 2003 (2)	22/34	14/29		9.5 %	1.34 [0.85, 2.10]
Subtotal (95% CI)	**34**	**29**		**9.5 %**	**1.34 [0.85, 2.10]**
Total events: 22 (Betahistine), 14 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.20)					
3 Other vertigo					
Canty 1981	11/15	6/17		5.7 %	2.08 [1.02, 4.24]
Conraux 1988	19/29	15/21		10.9 %	0.92 [0.63, 1.34]
Duphar 77054 1983	18/19	15/17		14.6 %	1.07 [0.88, 1.32]
Duphar H10800580M 1984	15/20	5/19		4.9 %	2.85 [1.29, 6.30]
Duphar H108906NL 1990	18/36	15/34		8.6 %	1.13 [0.69, 1.87]
Fischer 1985	33/36	32/37		15.4 %	1.06 [0.90, 1.25]
Oosterveld 1989	27/38	25/44		12.0 %	1.25 [0.90, 1.74]
Otto 2008	9/11	0/11		0.6 %	19.00 [1.24, 291.01]
Subtotal (95% CI)	**204**	**200**		**72.7 %**	**1.24 [0.97, 1.58]**
Total events: 150 (Betahistine), 113 (Placebo)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 22.07$, df = 7 (P = 0.002); $I^2 = 68\%$					
Test for overall effect: Z = 1.74 (P = 0.082)					
Total (95% CI)	**308**	**298**		**100.0 %**	**1.30 [1.05, 1.60]**
Total events: 212 (Betahistine), 150 (Placebo)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Betahistine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.07; Chi^2 = 30.84, df = 11 (P = 0.001); I^2 =64%					
Test for overall effect: Z = 2.46 (P = 0.014)					
Test for subgroup differences: Chi^2 = 0.62, df = 2 (P = 0.73), I^2 =0.0%					



(1) Meniere's subgroup

(2) BPPV subgroup

Analysis 1.2. Comparison 1 Betahistine versus placebo, Outcome 2 Proportion of patients with improvement according to global judgement of patient: subgrouped by drug dose.

Review: Betahistine for symptoms of vertigo

Comparison: 1 Betahistine versus placebo

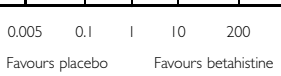
Outcome: 2 Proportion of patients with improvement according to global judgement of patient: subgrouped by drug dose

Study or subgroup	Betahistine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Betahistine dose less than 48 mg per day					
Burkin 1967	5/11	0/11		1.0 %	11.00 [0.68, 177.72]
Canty 1981	12/15	5/17		7.1 %	2.72 [1.25, 5.93]
Duphar 77054 1983	18/19	15/17		13.6 %	1.07 [0.88, 1.32]
Mira 2003	54/75	21/69		11.6 %	2.37 [1.61, 3.47]
Okamoto 1968	14/18	11/18		10.8 %	1.27 [0.82, 1.98]
Otto 2008	9/11	0/11		1.0 %	19.00 [1.24, 291.01]
Subtotal (95% CI)	**149**	**143**		**45.1 %**	**2.11 [1.03, 4.30]**
Total events: 112 (Betahistine), 52 (Placebo)					
Heterogeneity: Tau^2 = 0.53; Chi^2 = 47.17, df = 5 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 2.05 (P = 0.040)					
2 Betahistine dose 48 mg or over per day					
Conraux 1988	19/29	15/21		11.6 %	0.92 [0.63, 1.34]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Betahistine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Duphar H10800580M 1984	15/20	5/19		7.0 %	2.85 [1.29, 6.30]
Duphar H108906NL 1990	18/36	15/34		10.1 %	1.13 [0.69, 1.87]
Fischer 1985	33/36	32/37		13.9 %	1.06 [0.90, 1.25]
Oosterveld 1989	27/38	25/44		12.2 %	1.25 [0.90, 1.74]
Subtotal (95% CI)	**159**	**155**		**54.9 %**	**1.16 [0.92, 1.48]**
Total events: 112 (Betahistine), 92 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 8.64, df = 4 (P = 0.07); I^2 =54%					
Test for overall effect: Z = 1.23 (P = 0.22)					
Total (95% CI)	**308**	**298**		**100.0 %**	**1.45 [1.09, 1.94]**
Total events: 224 (Betahistine), 144 (Placebo)					
Heterogeneity: Tau^2 = 0.15; Chi^2 = 53.44, df = 10 (P<0.00001); I^2 =81%					
Test for overall effect: Z = 2.52 (P = 0.012)					
Test for subgroup differences: Chi^2 = 2.41, df = 1 (P = 0.12), I^2 =58%					

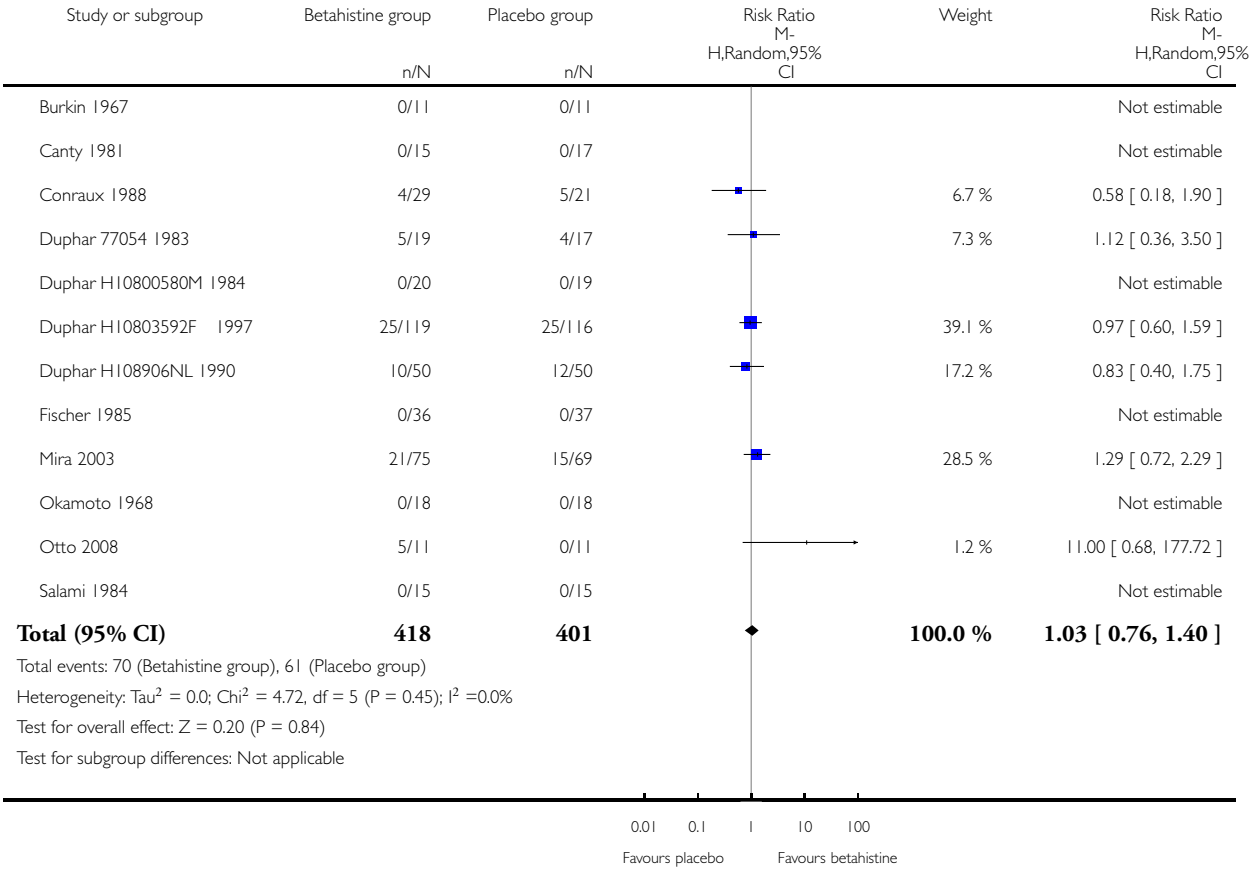


Analysis 1.3. Comparison 1 Betahistine versus placebo, Outcome 3 Proportion of patients with adverse effects.

Review: Betahistine for symptoms of vertigo

Comparison: 1 Betahistine versus placebo

Outcome: 3 Proportion of patients with adverse effects



Analysis 1.4. Comparison 1 Betahistine versus placebo, Outcome 4 Proportion of patients with upper gastrointestinal adverse effects.

Review: Betahistine for symptoms of vertigo

Comparison: 1 Betahistine versus placebo

Outcome: 4 Proportion of patients with upper gastrointestinal adverse effects

Study or subgroup	Betahistine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Conraux 1988	4/29	2/21		17.2 %	1.45 [0.29, 7.19]
Duphar 77054 1983	2/19	2/17		13.4 %	0.89 [0.14, 5.68]
Duphar H10803592F 1997	7/119	1/116		10.8 %	6.82 [0.85, 54.60]
Duphar H108906NL 1990	7/50	7/50		37.8 %	1.00 [0.38, 2.64]
Mira 2003	2/75	3/69		14.6 %	0.61 [0.11, 3.56]
Otto 2008	4/11	0/11		6.2 %	9.00 [0.54, 149.50]
Total (95% CI)	**303**	**284**		**100.0 %**	**1.38 [0.67, 2.82]**

Total events: 26 (Betahistine), 15 (Placebo)

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 5.74$, df = 5 (P = 0.33); $I^2 = 13\%$

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Betahistine versus placebo, Outcome 5 Proportion of patients with headache.

Review: Betahistine for symptoms of vertigo

Comparison: 1 Betahistine versus placebo

Outcome: 5 Proportion of patients with headache

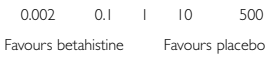
Study or subgroup	Betahistine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Duphar 77054 1983	0/19	1/17		18.0 %	0.30 [0.01, 6.91]
Duphar H10803592F 1997	6/119	11/116		36.5 %	0.53 [0.20, 1.39]
Duphar H108906NL 1990	0/50	2/50		18.8 %	0.20 [0.01, 4.06]
Mira 2003	11/75	1/69		26.7 %	10.12 [1.34, 76.35]
Total (95% CI)	**263**	**252**		**100.0 %**	**0.88 [0.15, 5.19]**

Total events: 17 (Betahistine), 15 (Placebo)

Heterogeneity: $Tau^2 = 2.02$; $Chi^2 = 8.61$, df = 3 (P = 0.03); $I^2 = 65\%$

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

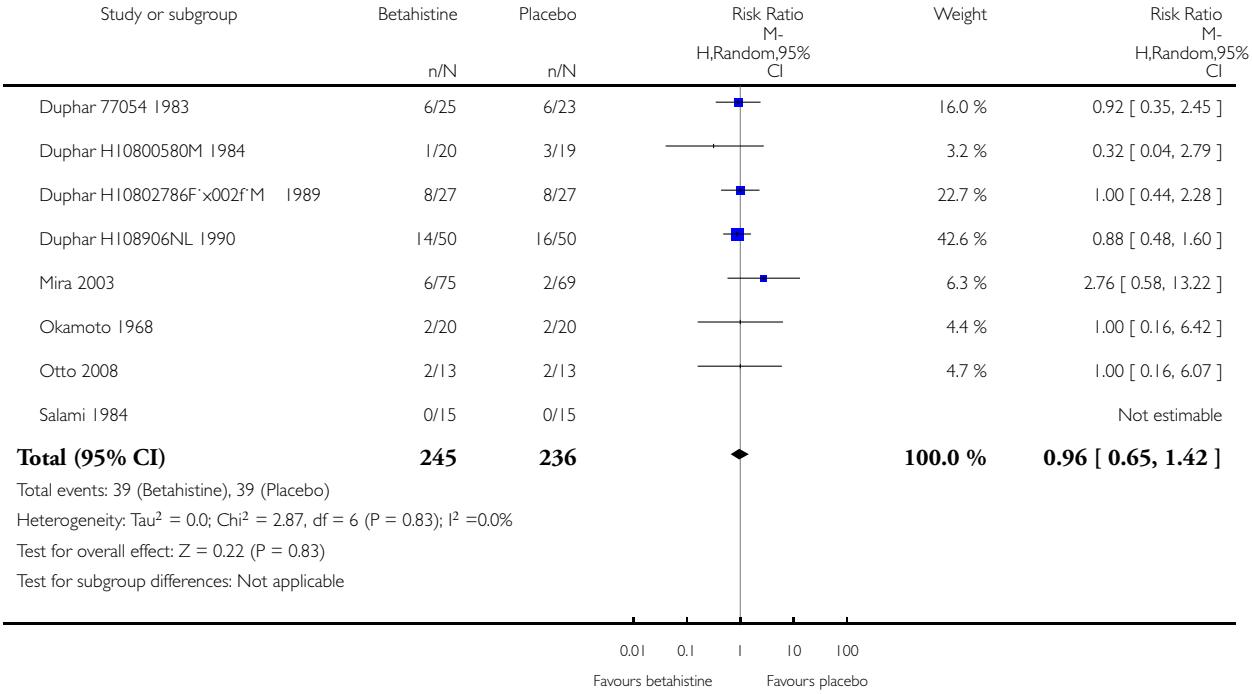


Analysis 1.6. Comparison 1 Betahistine versus placebo, Outcome 6 Withdrawal from study.

Review: Betahistine for symptoms of vertigo

Comparison: 1 Betahistine versus placebo

Outcome: 6 Withdrawal from study



APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
#1 MeSH descriptor: [Dizziness] explode all trees #2 MeSH descriptor: [Vertigo] explode all trees #3 MeSH descriptor: [Meniere Disease] explode all trees	#1 "Dizziness"[Majr] #2 "Vertigo"[Mesh] #3 "Meniere Disease"[Mesh] #4 (vertig* or bppv or meniere* or vestibular or endolymphatic and hydrops or	1 *dizziness/ 2 exp vertigo/ 3 exp Meniere disease/ 4 (vertig* or bppv or meniere* or vestibular or (endolymphatic and hydrops) or

(*Continued*)

#4 vertig* or bppv or meniere* or vestibular or (endolymphatic and hydrops) or (labyrinth and hydrops) or (labyrinth and syndrome) or (cochlea and hydrops) #5 lightheaded* or imbalance or disorientat* or dizzy or dizziness or (self next motion) or (illusion* near movement*) #6 #1 or #2 or #3 or #4 or #5 #7 MeSH descriptor: [Betahistine] explode all trees #8 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 or (BY next vertin) #9 #7 or #8 #10 #6 and #9	(labyrinth and hydrops) or (labyrinth and syndrome) or (cochlea and hydrops)) #5 (lightheaded* or imbalance or disorientat* or dizzy or dizziness or (self and motion) or (illusion* and movement*)) #6 (#1 OR #2 OR #3 OR #4 OR #5) #7 "Betahistine"[Mesh] #8 (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 or "BY vertin" or BY-vertin) #9 #7 OR #8 #10 (#9 AND #6)	(labyrinth and hydrops) or (labyrinth and syndrome) or (cochlea and hydrops)).tw 5 (lightheaded* or imbalance or disorientat* or dizzy or dizziness or (self adj6 motion) or (illusion* adj6 movement*)).tw 6 1 or 2 or 3 or 4 or 5 7 exp betahistine/ 8 (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 or (BY adj6 vertin)).tw 9 7 or 8 10 6 and 9
CINAHL (EBSCO)	**Web of Science (Web of Knowledge)**	**Trial Registries**
S1 (MM "Dizziness") S2 (MH "Vertigo") S3 (MH "Endolymphatic Hydrops+") OR (MH "Meniere's Disease") S4 TX vertig* or bppv or meniere* or vestibular or (endolymphatic and hydrops) or (labyrinth and hydrops) or (labyrinth and syndrome) or (cochlea and hydrops) S5 TX lightheaded* or imbalance or disorientat* or dizzy or dizziness or (self n6 motion) or (illusion* n6 movement*) S6 S1 OR S2 OR S3 OR S4 OR S5 S7 TX 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 or (BY n6 vertin) S8 S6 AND S7	#1 TS=(vertig* or bppv or meniere* or vestibular or (endolymphatic and hydrops) or (labyrinth and hydrops) or (labyrinth and syndrome) or (cochlea and hydrops)) #2 TS=(lightheaded* or imbalance or disorientat* or dizzy or dizziness or (self and motion) or (illusion* and movement*)) #3 #2 OR #1 #4 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 or "by vertin" or by-vertin) #5 #4 AND #3	**ClinicalTrials.gov** (vertigo OR vertiginous OR bppv OR meniere OR menieres OR vestibular OR dizzy OR dizziness) AND (betahistine OR betahistin OR serc OR betaserc) **ICTRP** betahistine AND Meniere* OR serc AND Meniere* OR betahistine and vertigo* OR serc AND vertigo* OR dizziness AND betahistine OR dizziness AND serc OR dizzy AND betahistine OR dizzy AND serc OR vestibular AND betahistine OR vestibular AND serc OR bppv AND betahistine OR bppv AND serc

CONTRIBUTIONS OF AUTHORS

LM obtained studies. LM and KH selected studies, extracted data and assessed risk of bias. LM entered data into RevMan 5, and carried out and interpreted the analysis. AS provided advice as needed throughout. LM, KH and AS drafted the final review. LM has responsibility for updating and maintaining the review.

DECLARATIONS OF INTEREST

Louisa Murdin has no interests to declare.

Kiran Hussain has no interests to declare.

Anne Schilder is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review. Her evidENT team at UCL is supported by her NIHR Research Professorship award with the remit to develop a UK infrastructure and programme of clinical research in ENT, Hearing and Balance. Her institution has received a grant from GSK for a study on the microbiology of acute tympanostomy tube otorrhoea.

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Infrastructure funding for Cochrane ENT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added 'withdrawal from study' as an outcome measure in addition to proportion of patients with adverse effects.

We have promoted 'Proportion of patients with adverse effects' from a secondary to a primary outcome measure.

We removed 'double-blinded' from the inclusion criteria for types of studies. Level of blinding was dealt with in our 'Risk of bias' assessments, as is standard practice.

We have described the GRADE methodology and process for creating the 'Summary of findings' table in the Methods section.

INDEX TERMS

Medical Subject Headings (MeSH)

Benign Paroxysmal Positional Vertigo [drug therapy]; Betahistine [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Vertigo [*drug therapy]

MeSH check words

Humans