ClinicalEvidence

Menière's disease

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ABSTRACT

INTRODUCTION: Menière's disease causes recurrent vertigo, hearing loss, tinnitus, and fullness or pressure in the ear, which mainly affects adults aged 40–60 years. Menière's disease is at first progressive but fluctuating, and episodes can occur in clusters. Vertigo usually resolves but hearing deteriorates, and symptoms other than hearing loss and tinnitus usually improve regardless of treatment. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for acute attacks of Menière's disease; and of interventions to prevent attacks and delay disease progression of Menière's disease? We searched: Medline, Embase, The Cochrane Library and other important databases up to January 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 17 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticholinergics, benzodiazepines, betahistine, cinnarizine, dietary modification, diuretics, phenothiazines, psychological support, trimetazidine, vestibular rehabilitation.

QUESTIONS

INTERVENTIONS

Key points

- Menière's disease causes recurrent vertigo, hearing loss, tinnitus, and fullness or pressure in the ear, which mainly affects adults aged 40–60 years.

  Menière's disease is at first progressive but fluctuating, and episodes can occur in clusters.

  Vertigo usually resolves but hearing deteriorates, and symptoms other than hearing loss and tinnitus usually improve regardless of treatment.

- We do not know whether anticholinergic drugs, benzodiazepines, phenothiazines, cinnarizine, or betahistine improve symptoms in an acute attack of Menière's disease, as no good quality studies have been found.

- Betahistine seems to be no more effective than placebo at preventing hearing loss in people with Menière's disease.

  We do not know whether betahistine reduces the frequency or severity of vertigo, tinnitus or aural fullness.

  We do not know whether diuretics, trimetazidine, dietary modification, psychological support, or vestibular rehabilitation improve tinnitus or hearing, or reduce the frequency of attacks of Menière's disease.

DEFINITION

Menière's disease is characterised by recurrent episodes of spontaneous rotational vertigo, sensorineural hearing loss, tinnitus, and a feeling of fullness or pressure in the ear. It may be unilateral or bilateral. Acute episodes can occur in clusters of about 6–11 a year, although remission may last several months. [1] The diagnosis is made clinically. [2] It is important to distinguish Menière's disease from other types of vertigo that might occur independently with hearing loss and tinnitus, and respond differently to treatment (e.g. benign positional vertigo, acute labyrinthitis). Strict diag-

nostic criteria help to identify the condition. In this review, we have applied the classification of the American Academy of Otolaryngology — Head and Neck Surgery to assess the diagnostic rigour used in RCTs (see table 1, p 9). [3] [4] [5]

INCIDENCE/ PREVALENCE

Menière's disease is most common between 40–60 years of age, although younger people may be affected. [6] [7] In Europe, the incidence is about 50–200/100 000 a year. A survey of general practitioner records of 27 365 people in the UK in the 1950s found an incidence of 43 affected people in a 1 year period (157/100 000). [8] Diagnostic criteria were not defined in this survey. A survey of over 8 million people in 1973 in Sweden found an incidence of 46/100 000 a year with diagnosis strictly based on the triad of vertigo, hearing loss, and tinnitus. [9] From smaller studies, the incidence appears to be lower in Japan (17/100 000, based on national surveys of hospital attendances in 1977, 1982, and 1990) [7] and in Uganda. [10]

AETIOLOGY/ RISK FACTORS

Menière's disease is associated with endolymphatic hydrops (raised endolymph pressure in the membranous labyrinth of the inner ear), [11] but a causal relationship remains unproved. [12] Specific disorders associated with hydrops (such as temporal bone fracture, syphilis, hypothyroidism, Cogan's syndrome, and Mondini dysplasia) can produce symptoms similar to those of Menière's disease.

PROGNOSIS

Menière's disease is at first progressive but fluctuates unpredictably. It is difficult to distinguish natural resolution from the effects of treatment. Significant improvement in vertigo is usually seen in the placebo arm of RCTs. [13] [14] Acute attacks of vertigo often increase in frequency during the first few years after presentation and then decrease in frequency in association with sustained deterioration in hearing. [6] In most people, vertiginous episodes eventually cease completely. [15] In one 20 year cohort study in 34 people, 28 (82%) people had at least moderate hearing loss (mean pure tone hearing loss > 50 dB) and 16 (47%) developed bilateral disease. [1] Symptoms other than hearing loss improve in 60–80% of people irrespective of treatment. [16]

AIMS OF INTERVENTION

To prevent attacks of Menière's disease; to reduce the severity of vertigo in acute attacks; to relieve chronic symptoms of hearing loss and tinnitus; to improve quality of life, with minimum adverse effects of treatment.

OUTCOMES

Frequency and severity of acute attacks of vertigo; hearing acuity; severity of tinnitus; sensation of aural fullness; functional impairment and quality of life; adverse effects of treatment.

METHODS

BMJ Clinical Evidence search and appraisal January 2006. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2006, Embase 1980 to January 2006, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2005, Issue 4. Additional searches were carried out using the following websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow up required to include studies. We excluded all studies described as “open”, “open label”, or not blinded, unless blinding was impossible. We use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. The authors excluded RCTs that did not comply with the American Academy of Otolaryngology — Head and Neck Surgery diagnostic criteria. [3] [4] [5] We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 9).

QUESTION What are the effects of treatments for acute attacks of Menière's disease?

OPTION ANTICHOLINERGICS

Symptom relief

Compared with placebo The anticholinergic glycopyrrolate may be more effective at reducing vertigo at 4 weeks (very low-quality evidence).

Note

We found no direct information from RCTs about the effects of anticholinergics for the treatment of people with acute attacks of Menière's disease.

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: We found no systematic review or RCTs. We found one non-randomised trial (see comment below). [17]

Harms: The non-randomised trial gave no information on adverse effects. [17]

Comment: The non-randomised trial (37 people with definite Menière's disease) compared an anticholinergic (glycopyrrolate 2 mg twice daily as required) versus placebo for 4 weeks. [17] It found that glycopyrrolate significantly reduced the severity of vertigo and its impact on quality of life compared with placebo (Dizziness Handicap Inventory, a validated symptom score, [18] change from baseline to end of trial: 76 to 37 points with glycopyrrolate *v* 73 to 75 points with placebo; $P < 0.001$). The lack of randomisation means that this result should be interpreted with caution.

OPTION BENZODIAZEPINES

We found no direct information from RCTs about the effects of benzodiazepines in the treatment of people with acute attacks of Menière's disease.

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION BETAHISTINE

We found no direct information from RCTs about the effects of betahistine in the treatment of people with acute attacks of Menière's disease.

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION CINNARIZINE New

We found no direct information from RCTs about the effects of cinnarizine in the treatment of people with acute attacks of Menière's disease.

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

OPTION PHENOTHIAZINES New

We found no direct information from RCTs about the effects of phenothiazines in the treatment of people with acute attacks of Menière's disease.

For GRADE evaluation of Menière's disease, see table, p 9 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: None.

QUESTION **What are the effects of interventions to prevent attacks and delay disease progression of Menière's disease?**

OPTION **BETAHISTINE FOR VERTIGO OR TINNITUS OR AURAL FULLNESS**

Prevention of attacks
Compared with placebo We don't know whether betahistine is more effective at preventing attacks of vertigo, tinnitus, or aural fullness in people with Menière's disease (very low-quality evidence).

Compared with trimetazidine We don't know whether betahistine is more effective at reducing attacks of vertigo, tinnitus, hearing loss, or aural fullness in people with Menière's disease (very low-quality evidence).

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits:

Betahistine versus placebo:
We found one systematic review [19] (search date 1999, 6 RCTs, [13] [20] [21] [22] [23] [24] 162 people) and one subsequent RCT, [25] which compared betahistine versus placebo in people with Menière's disease. The review evaluated the diagnostic accuracy of included studies on the basis of the robustness of methods used for diagnosis. [19] It noted that diagnostic criteria varied among studies, and none used American Academy of Otolaryngology — Head and Neck Surgery guidelines (see table 1, p 9). The review did not include a meta-analysis because of heterogeneity among trials (see comment below). [19] The first RCT identified by the review (30 people with a diagnosis consistent with possible Menière's disease) found that betahistine (8 mg three times daily) significantly reduced the severity of vertigo after 6 weeks compared with placebo (results presented graphically; P = 0.0001), tinnitus (results presented graphically; P = 0.001), and aural fullness (results presented graphically; P = 0.02). [20] The second RCT identified by the review (35 people with a diagnosis consistent with possible Menière's disease, crossover design) found no significant difference between betahistine (24 mg three times daily in a slow release formulation) and placebo in tinnitus (results presented graphically; P = 0.68) or aural fullness (results presented graphically; P = 0.63) after 16 weeks. [13] Vertigo was not adequately assessed. Crossover studies are difficult to interpret if used to evaluate the effects of treatments on conditions that fluctuate in intensity or if interventions have prolonged effects. [26] Menière's disease is not a stable condition and it is unknown whether any effects of betahistine are prolonged. The third RCT identified by the review (16/36 [44%] people had a diagnosis consistent with possible Menière's disease) found no significant difference between betahistine (18 mg twice daily) and placebo after 2 weeks on the proportion of people reporting improved vertigo or tinnitus (vertigo: RR 1.17, 95% CI 0.86 to 1.58; tinnitus: RR 2.4, 95% CI 0.11 to 51.32; absolute numbers not reported for either outcome). [21] The fourth RCT identified by the review (10 people with a diagnosis consistent with possible Menière's disease) found no significant difference between betahistine (8 mg three times daily) and placebo in the proportion of people with improved vertigo, tinnitus, or aural fullness over 6–12 months (improved vertigo: RR 5.0, 95% CI 0.3 to 84; absolute numbers not reported). [22] The remaining two RCTs identified by the review reported insufficient detail to confirm reliably that the participants had Menière's disease. [23] [24] The subsequent RCT (81 people with possible or probable Menière's disease) found that betahistine (8 mg twice daily) significantly reduced the frequency of attacks of vertigo and increased the proportion of people reporting a reduction in severity of vertigo over 3 months compared with placebo (results presented graphically; decrease in vertigo attacks: about 65% with betahistine *v* about 20% with placebo, P < 0.05; reduced intensity score read from graph: about 67% with betahistine *v* about 30% with placebo, P < 0.03). [25] However, the results should be interpreted with caution because it was not clear whether other outcomes were assessed but not reported. The RCT did not report the number of people with each outcome, severity of symptoms, or effects on hearing. [25]

Betahistine versus trimetazidine:
See benefits of trimetazidine, p 6 .

Harms:

Betahistine versus placebo:
None of the RCTs identified by the review reported any significant adverse effects. [19] The subsequent RCT (81 people) found that betahistine increased headache compared with placebo (5/41 [12.2%] with betahistine *v* 0/40 [0%] with placebo; P value and CI not reported). [25] It found no significant difference between treatments for overall adverse effects (28% with betahistine *v* 22% with placebo; P value and CI not reported).

Betahistine versus trimetazidine:
No significant adverse effects were reported in the RCTs. [27] [28]

Comment: The systematic review reported that "we found no trials with a low risk of methodological bias which used the highest level of diagnostic criteria and outcome measures". [19] It stated that the lack of diagnostic certainty made it inappropriate to combine results. [19] Bias from selective reporting of outcome measures cannot be excluded in the subsequent RCT comparing betahistine versus placebo. [25]

OPTION DIETARY MODIFICATION

We found no clinically important results from RCTs investigating the effects of dietary modification (including salt reduction) in preventing attacks or delaying disease progression in people with Menière's disease.

For GRADE evaluation of interventions for Menière's disease, **see table, p 9 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: It has been suggested that a low salt diet reduces endolymphatic pressure in endolymphatic hydrops, [29] but we found no evidence from RCTs to support or refute this.

OPTION DIURETICS

Prevention of attacks
Compared with placebo We don't know whether the diuretic triamterene plus hydrochlorothiazide is more effective at reducing tinnitus, vertigo or at improving hearing at 17 weeks in people with Menière's disease (very low-quality evidence).

Note
We found no direct information from RCTs about the effects of diuretics on delaying disease progression in people with Menière's disease.

For GRADE evaluation of inerventions for Menière's disease, **see table, p 9 .**

Benefits: We found no systematic review but found one crossover RCT (33 people with possible Menière's disease) comparing a diuretic (triamterene 50 mg plus hydrochlorothiazide 25 mg) versus placebo. [30] It found no significant difference in audiological change in hearing over 17 weeks (speech hearing scores: speech intensity required for 50% discrimination (dB_{50}); 48.6 with diuretic *v* 50.1 with placebo; P = 0.28; maximum speech discrimination (Max. disc.); 88.9 with diuretic *v* 89.9 with placebo; P = 0.29; speech intensity at maximum discrimination (dB_{max}); 90.4 with diuretic *v* 91.9 with placebo; P = 0.25; absolute numbers not reported for any hearing score). However, the trial may have lacked power to detect a clinically important difference. The trial provided insufficient data to assess effects on vertigo and tinnitus. In the RCT, the frequency of vertigo attacks was reduced and tinnitus was unchanged, but valid statistical analyses cannot be performed because the study presented only the mean values for categorical data. [30]

Harms: The RCT gave no information on adverse effects. [30]

Comment: None.

OPTION PSYCHOLOGICAL SUPPORT

We found no direct information from RCTs about the effects of psychological support, such as reassurance, in preventing attacks or delaying disease progression in people with Menière's disease.

For GRADE evaluation of interventions for Menière's disease, **see table, p 9 .**

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: Symptomatic improvement is seen with all treatments for Menière's disease, including placebo [16] [31] or being put on a waiting list for surgery. [32] Such improvements may be attributed to the psychological support of receiving treatment, but have not been distinguished from improvements attributable to the natural history of Menière's disease.

OPTION TRIMETAZIDINE

Prevention of attacks
Compared with betahistine We don't know whether trimetazidine is more effective at reducing attacks of vertigo, tinnitus, hearing loss, or aural fullness in people with Menière's disease (very low-quality evidence).

Note
We found no direct information from RCTs about whether trimetazidine is better than no active treatment in preventing attacks of Menière's disease, or about the effects of trimetazidine on disease progression.

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: We found no systematic review.

Trimetazidine versus placebo:
We found no RCTs.

Trimetazidine versus betahistine:
We found two RCTs. [27] [28] The first RCT (20 people with definite or probable Menière's disease) compared trimetazidine (20 mg three times daily) versus betahistine (8 mg three times daily) over 3 months. [27] It found no significant difference in hearing, tinnitus, aural fullness, or quality of life (RR for improved quality of life 1.0, 95% CI 0.34 to 2.93; absolute numbers not reported). Trimetazidine significantly increased the proportion of people reporting that the duration of vertigo was "substantially better or cured" or reporting that the intensity of vertigo was "substantially better or cured" compared with betahistine (vertigo improved: RR 1.8, 95% CI 1.0 to 3.2; vertigo intensity: RR 1.7, 95% CI 1.0 to 2.8; absolute numbers not reported). Trimetazidine also significantly improved the global impression of vertigo scale compared with betahistine, but it is not clear whether this scale has been validated (RR for improvement 2.5, 95% CI 1.17 to 5.3; absolute numbers not reported). [27] The second RCT (45 people with possible Menière's disease) compared trimetazidine (20 mg three times daily) versus betahistine (12 mg three times daily) over 2 months and found no significant difference in hearing or tinnitus. [28] There was no significant difference between trimetazidine and betahistine at improving vertigo intensity (1.9 with trimetazidine *v* 2.0 with betahistine; P value reported as non-significant). A beneficial effect of trimetazidine on vertigo intensity was reported, but this was not confirmed by analysis of the available data (P = 0.23; 2 sided Fisher's exact test; absolute numbers not reported). [28]

Harms: No clinically important adverse effects were reported in the RCTs (results not reported). [27] [28]

Comment: None.

OPTION VESTIBULAR REHABILITATION

We found no direct information from RCTs about the effects of vestibular rehabilitation in preventing attacks or delaying disease progression in people with Menière's disease.

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: We found no systematic review or RCTs about the effects of vestibular rehabilitation.

Harms: We found no RCTs.

Comment: None.

OPTION BETAHISTINE FOR HEARING LOSS

Prevention of attacks
Compared with placebo Betahistine may be no more effective at improving hearing in people with Menière's disease (very low-quality evidence).

Compared with trimetazidine We don't know whether betahistine is more effective at improving hearing in people with Menière's disease (very low-quality evidence).

For GRADE evaluation of interventions for Menière's disease, see table, p 9 .

Benefits: **Betahistine versus placebo:**
We found one systematic review (search date 1999) [19] which included four RCTs [13] [20] [21] [22] that assessed hearing loss measured by pure tone audiogram. It did not pool data and the review

was narrative. None of the RCTs found any change in hearing as assessed by pure tone audiograms (results not reported). [13] [20] [21] [22] However, all of the RCTs were of limited quality (see benefits of betahistine for vertigo or tinnitus or aural fullness, p 4). One RCT [13] was crossover design, in one of the RCTs [21] 22/36 [61%] had normal hearing at the start of the trial, and another RCT [22] was very small (10 people).

Betahistine versus trimetazidine:
See benefits of trimetazidine, p 6 .

Harms:

Betahistine versus placebo:
See harms of betahistine for vertigo or tinnitus or aural fullness, p 4 .

Betahistine versus trimetazidine:
See harms of betahistine for vertigo or tinnitus or aural fullness, p 4 .

Comment: See comments of betahistine for vertigo or tinnitus or aural fullness, p 4 .

GLOSSARY

Cogan's syndrome Episodic vertigo of the Menière's type, hearing loss, and interstitial keratitis, without syphilis. [5]
Mondini dysplasia A congenital deformity of the cochlea in which only the basal turns are present.
Vestibular rehabilitation Involves a series of exercises intended to improve the sense of balance through controlled movements of the head and body. [33] It is usually recommended for stable vestibular disorders. [34]
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Cinnarizine.
New option added Phenothiazines.

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Competing interests: AJ is the co-author of one systematic review referenced in this review. MT declares that he has no competing interests.

Disclaimer

TABLE 1 **American Academy of OtolaryngologyHead and Neck Surgery definition of the certainty of diagnosis of Menire's disease (see text).** [3] [4] [5]

Certain	Definite Menière's disease plus postmortem confirmation
Definite	Two or more episodes of vertigo* plus audiometrically confirmed sensorineural hearing loss; tinnitus or aural fullness plus other causes excluded
Probable	One episode of vertigo* plus audiometrically confirmed sensorineural hearing loss plus tinnitus or aural fullness; other causes excluded
Possible	Episodes of vertigo* with no hearing loss, or sensorineural hearing loss with dysequilibrium; other causes excluded

*Defined as spontaneous, rotational vertigo lasting more than 20 minutes.

TABLE **GRADE evaluation of interventions for Menière's disease**

Important outcomes	**Symptom relief, prevention of attacks, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for acute attacks of Menière's disease?									
1 (37) [17]	Symptom relief	Anticholinergics *v* placebo	4	–2	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results and for non-randomised study
What are the effects of interventions to prevent attacks and delay disease progression of Menière's disease?									
5 (192) [13] [20] [21] [22] [25]	Prevention of attacks	Betahistine *v* placebo	4	–3	–1	–2	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, methodology flaws, and uncertainty about diagnosis. Consistency point deducted for conflicting results. Directness point deducted for uncertainty about measurement of outcomes and for heterogeneity among RCTs
1 (33) [31]	Prevention of attacks	Diuretics *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, for incomplete reporting of results and for lack of statistical analysis
2 (65) [27] [28]	Prevention of attacks	Trimetazidine *v* betahistine	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results
4 (111) [13] [20] [21] [22]	Prevention of attacks	Betahistine *v* placebo	4	–3	–1	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for mthodological flaws. Consistency point deducted for heterogeneity among RCTs. Directness point deducted for uncertainty about diagnosis

Type of evidence: 4 = RCT; 2 = Observational.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.