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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 7
OBJECTIVES 8
METHODS 8
Figure 1. 9
Figure 2. 10
Figure 3. 11
RESULTS 12
DISCUSSION 19
AUTHORS' CONCLUSIONS 20
ACKNOWLEDGEMENTS 21
REFERENCES 22
CHARACTERISTICS OF STUDIES 24
DATA AND ANALYSES 32
Analysis 1.1. Comparison 1 Positive pressure therapy versus placebo, Outcome 1 Proportion of days with vertigo in 4 weeks: vertigo scores > 2. 33
Analysis 1.2. Comparison 1 Positive pressure therapy versus placebo, Outcome 2 Vertigo scores after 4 months. 33
Analysis 1.3. Comparison 1 Positive pressure therapy versus placebo, Outcome 3 Vertigo days in 4 months: vertigo scores > 2. 33
Analysis 1.4. Comparison 1 Positive pressure therapy versus placebo, Outcome 4 Vertigo frequency in the 8 weeks before and after 4 weeks of treatment. 34
Analysis 1.5. Comparison 1 Positive pressure therapy versus placebo, Outcome 5 VAS scores for vertigo after 8 weeks of treatment. 34
Analysis 1.6. Comparison 1 Positive pressure therapy versus placebo, Outcome 6 Loss or gain of hearing in 4 months (dB). 34
Analysis 1.7. Comparison 1 Positive pressure therapy versus placebo, Outcome 7 Cumulative activity score at 4 months. 34
Analysis 1.8. Comparison 1 Positive pressure therapy versus placebo, Outcome 8 Change in functional profile between 8 weeks before and after 4 weeks of treatment. 35
Analysis 1.9. Comparison 1 Positive pressure therapy versus placebo, Outcome 9 Sick days in 4 months. 35
ADDITIONAL TABLES 35
APPENDICES 36
CONTRIBUTIONS OF AUTHORS 39
DECLARATIONS OF INTEREST 39
SOURCES OF SUPPORT 39
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 39
INDEX TERMS 39

[Intervention Review]

Positive pressure therapy for Ménière's disease or syndrome

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ABSTRACT

Background

Ménière's disease is an incapacitating disease in which recurrent attacks of vertigo are accompanied by hearing loss, tinnitus and/or aural fullness, all of which are discontinuous and variable in intensity. A number of different therapies have been identified for patients with this disease, ranging from dietary measures (e.g. a low-salt diet) and medication (e.g. betahistine (Serc®), diuretics) to extensive surgery (e.g. endolymphatic sac surgery). The Meniett® low-pressure pulse generator (Medtronic ENT, 1999) is a device that is designed to generate a computer-controlled sequence of low-pressure (micro-pressure) pulses, which are thought to be transmitted to the vestibular system of the inner ear. The pressure pulse passes via a tympanostomy tube (grommet) to the middle ear, and hence to the inner ear via the round and/or oval window. The hypothesis is that these low-pressure pulses reduce endolymphatic hydrops.

Objectives

To assess the effects of positive pressure therapy (e.g. the Meniett device) on the symptoms of Ménière's disease or syndrome.

Search methods

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 6 June 2014.

Selection criteria

Randomised controlled trials (RCTs) comparing positive pressure therapy (using the Meniett or a similar device) with placebo in patients with Ménière's disease. The primary outcome was control of vertigo; secondary outcomes were loss or gain of hearing, severity of tinnitus, perception of aural fullness, functional level, complications or adverse effects, and sick days.

Data collection and analysis

Two authors independently selected studies, assessed risk of bias and extracted data. We contacted authors for additional data. Where possible, we pooled study results using a fixed-effect, mean difference (MD) meta-analysis and tested for statistical heterogeneity using both the Chi^2 test and I^2 statistic. This was only possible for the secondary outcomes loss or gain of hearing and sick days. We presented results using forest plots with 95% confidence intervals (CI).

Main results

We included five randomised clinical trials with 265 participants. All trials were prospective, double-blind, placebo-controlled randomised controlled trials on the effects of positive pressure therapy on vertigo complaints in Ménière's disease. Overall, the risk of bias varied: three out of five studies were at low risk, one was at unclear risk and one was at high risk of bias.

Control of vertigo

For the primary outcome, control of vertigo, it was not possible to pool data due to heterogeneity in the measurement of the outcome measures. In most studies, no significant difference was found between the positive pressure therapy group and the placebo group in vertigo scores or vertigo days. Only one study, at low risk of bias, showed a significant difference in one measure of vertigo control in favour of positive pressure therapy. In this study, the mean visual analogue scale (VAS) score for vertigo after eight weeks of treatment was 25.5 in the positive pressure therapy group and 46.6 in the placebo group (mean difference (MD) -21.10, 95% CI -35.47 to -6.73; scale not stated - presumed to be 0 to 100).

Secondary outcomes

For the secondary outcomes, we carried out two pooled analyses. We found statistically significant results for ***loss or gain of hearing*** . Hearing was 7.38 decibels better in the placebo group compared to the positive pressure therapy group (MD) (95% CI 2.51 to 12.25; two studies, 123 participants). The ***severity of tinnitus*** and ***perception of aural fullness*** were either not measured or inadequate data were provided in the included studies. For the secondary outcome ***functional level*** , it was not possible to perform a pooled analysis. One included study showed less functional impairment in the positive pressure group than the placebo group (AAO-HNS criteria, one- to six-point scale: MD -1.10, 95% CI -1.81 to -0.39, 40 participants); another study did not show any significant results. In addition to the predefined secondary outcome measures, we included ***sick days*** as an additional outcome measure, as two studies used this outcome measure and it is a complementary measurement of impairment due to Ménière's disease. We did not find a statistically significant difference in sick days. No ***complications or adverse effects*** were noted by any study.

Authors' conclusions

There is no evidence, from five included studies, to show that positive pressure therapy is effective for the symptoms of Ménière's disease. There is some moderate quality evidence, from two studies, that hearing levels are worse in patients who use this therapy. The positive pressure therapy device itself is minimally invasive. However, in order to use it, a tympanostomy tube (grommet) needs to be inserted, with the associated risks. These include the risks of anaesthesia, the general risks of any surgery and the specific risks of otorrhoea and tympanosclerosis associated with the insertion of a tympanostomy tube. Notwithstanding these comments, no complications or adverse effects were noted in any of the included studies.

PLAIN LANGUAGE SUMMARY

Positive pressure therapy for Ménière's disease or syndrome

Background

Ménière's disease is a disorder of the inner ear, which results in vertigo, hearing loss and tinnitus. When it is secondary to another known inner ear disorder, it is called Ménière's syndrome. A number of different treatments have been used for patients with this disease, ranging from dietary measures (e.g. a low-salt diet) and medication (e.g. betahistine or diuretics) to extensive surgery. However, Ménière's disease has a fluctuating natural course with remissions and exacerbations, which makes the evaluation of treatments difficult.

Positive pressure therapy uses a device (such as the Meniett®) placed in the external ear to generate a sequence of low-pressure (micro-pressure) pulses. These pulses are thought to be transmitted to the vestibular system of the inner ear and to influence inner ear pressure. The device has been proposed as a second-level therapy for Ménière's disease. In order to use the device a patient needs to have a tympanostomy tube (grommet) inserted through their eardrum.

Study characteristics

In this review, we included five randomised controlled trials, with a total of 265 participants. All participants had Ménière's disease and their ages ranged from 19 to 74 years. In all of the studies positive pressure therapy was compared with a placebo device.

Key results

For our primary outcome, control of vertigo, we could not combine the results from the different studies because of differences in the way the outcome was measured. None of the included studies showed significant differences between the active groups and placebo groups in terms of vertigo days. Only one study found significantly lower subjective scores for vertigo in favour of the positive pressure therapy group when compared to the placebo group.

When we combined the results from two studies we found that after treatment patients in the placebo group had better hearing levels compared to those in the positive pressure therapy group. The severity of tinnitus and perception of aural fullness were either not measured or the included studies did not provide enough information for us to comment on them. We did not find an overall statistically significant result for functional level. We also looked at 'sick days' but we did not find a statistically significant difference between groups in the two studies that measured this. No complications or adverse effects were noted by any study.

Quality of the evidence

Overall, the studies were at varied risk of bias: three out of five studies were at low risk, one was at unclear risk and one was at high risk of bias. The evidence is up to date to June 2014.

Conclusions

In conclusion, this review has not found adequate evidence to prove the effectiveness of positive pressure therapy. Further research is needed.

Summary of findings for the main comparison. Positive pressure therapy versus placebo for Ménière's disease or syndrome

Positive pressure therapy versus placebo for Ménière's disease or syndrome						
Patient or population: patients with Ménière's disease or syndrome **Settings:** ENT departments **Intervention:** positive pressure therapy versus placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Positive pressure therapy**				
Proportion of days with vertigo in 4 weeks: vertigo scores > 2 Follow-up: mean 4 weeks	The mean proportion of days with vertigo in 4 weeks (vertigo scores > 2) in the control groups was **0.11**	The mean proportion of days with vertigo in 4 weeks (vertigo scores > 2) in the intervention groups was **0.01 lower** (0.08 lower to 0.06 higher)		62 (1 study)	⊕⊕⊕⊖ **moderate** 1,2,3,4,5,6	
Cumulative vertigo scores after 4 months Follow-up: mean 4 months	The mean cumulative vertigo score after 4 months in the control groups was **19.23**	The mean cumulative vertigo score after 4 months in the intervention groups was **3.68 lower** (14.24 lower to 6.88 higher)		68 (1 study)	⊕⊕⊕⊖ **moderate** 1,7	
Vertigo days in 4 months: vertigo scores > 2 Follow-up: mean 4 months	The mean vertigo days in 4 months (vertigo scores > 2) in the control groups was **5.52**	The mean vertigo days in 4 months (vertigo scores > 2) in the intervention groups was **1.55 lower** (5.4 lower to 2.3 higher)		68 (1 study)	⊕⊕⊕⊖ **moderate** 1,7	
Vertigo frequency in the 8 weeks before and after 4 weeks of treatment Follow-up: mean 12 weeks	The mean vertigo frequency in the 8 weeks before and after 4 weeks of treatment in the control groups was **4.0**	The mean vertigo frequency in the 8 weeks before and after 4 weeks of treatment in the intervention groups was **2.10 lower** (5.25 lower to 1.05 higher)		40 (1 study)	⊕⊕⊕⊖ **moderate** 1,2,8,9	

VAS scores for vertigo after 8 weeks of treatment Follow-up: mean 12 weeks	The mean VAS score for vertigo after 8 weeks of treatment in the control groups was **46.6**	The mean VAS score for vertigo after 8 weeks of treatment in the intervention groups was **21.1 lower** (35.47 to 6.73 lower)		40 (1 study)	⊕⊕⊕⊖ **moderate** 1,2,8,9
Loss or gain of hearing in 4 months (dB) Follow-up: mean 4 months	The mean hearing threshold at 0.25 kHz to 1 kHz in 4 months in the control groups was **44.4**	The mean loss or gain of hearing in 4 months in the intervention groups was **7.38 higher** (2.51 to 12.25 higher)		123 (2 studies)	⊕⊕⊕⊖ **moderate** 1,2,3,4,5,6,7
Cumulative activity score Follow-up: mean 4 months	The mean activity score after 4 months in the control group was **20.23**	The mean cumulative activity score in the intervention groups was **7.18 lower** (17.68 lower to 3.32 higher)		68 (1 study)	⊕⊕⊕⊖ **moderate** 1,7
Change in functional profile in the 8 weeks before and after 4 weeks of treatment Follow-up: mean 12 weeks	The mean change in functional profile in the 8 weeks before and after 4 weeks of treatment in the control group was **3.5**	The mean change in functional profile in the 8 weeks before and after 4 weeks of treatment in the intervention group was **1.10 lower** (1.81 to 0.39 lower)		40 (1 study)	⊕⊕⊕⊖ **moderate** 1,2,8,9
Sick days in 4 months	The mean sick days in 4 months in the control groups was **1.73**	The mean sick days in 4 months in the intervention groups was **1.03 lower** (3.59 lower to 1.53 higher)		125 (2 studies)	⊕⊕⊕⊖ **moderate** 1,2,3,4,5,6,7

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Per-protocol analysis while claiming an intention-to-treat analysis.
[2]No description of reasons for drop-out or treatment failure.
[3]Overestimation of the effect of the placebo device (and underestimation of the effect of the Meniett device), because most treatment failures dropped out of the placebo group.
[4]The decrease in days with vertigo is not significantly different in the treatment group compared to the placebo group in any of the follow-up months.

[5]Additional low-sodium diet.
[6]A high proportion of participants used diuretics (80% in the placebo group and 73% in the active treatment group).
[7]Additional use of betahistine.
[8]Unclear statistics.
[9]Use of frequencies before insertion of the ventilation tube and after treatment, while claiming to rule out the effect of the ventilation tube.

BACKGROUND

Description of the condition

Ménière's disease is an incapacitating disease in which recurrent attacks of vertigo are accompanied by hearing loss, tinnitus and/or aural fullness. The attacks of vertigo may follow each other with intervals of days, weeks or even months. Usually, these become less severe and disappear after two to eight years in 60% to 80% of sufferers with profound lasting hearing loss and tinnitus (Portmann 1980; Silverstein 1989). However, there is great variability in the presentation and natural course of the disease. When no known cause of the disease is identified, the term Ménière's *disease* is applicable. When the symptoms are secondary to a known disease (e.g. meningitis), the term Ménière's *syndrome* is used.

Few articles have been published on the epidemiology of Ménière's disease. Great variation exists in the published reports of the incidence and prevalence of Ménière's disease, ranging from 17 cases per 100,000 population in Japan (Nakae 1984) to 46 cases per 100,000 population in Sweden (Stahle 1978). There seems to be a slight female preponderance, with up to 1.3 times more women affected than men. The disease is more common in adults in their fourth and fifth decade of life (Kotimaki 1999; Sajjadi 2008). The frequency of bilateral disease is unclear. Published reports vary greatly, from 2% to 78% (Balkany 1980). In a large population study by Kitahara in Japan, bilaterality of disease was noted in 9.1% of patients in their first year of experiencing symptoms. This increased steadily to 41.5% after 20 years of disease (Kitahara 1991).

In 1861, Prosper Ménière first recognised that this disorder originated from the inner ear (the membranous labyrinth), but wrongly attributed the cause to haemorrhage (Meniere 1861). In 1938, Hallpike and Yamakawa independently described a hydrops (i.e. accumulation of fluid) of the endolymphatic system in patients with Ménière's disease (Hallpike 1938; Yamakawa 1938). In 1965, Kimura introduced an experimental model in which an endolymphatic hydrops was produced in guinea pigs after surgical obliteration of the endolymphatic sac and duct (Kimura 1967). Endolymphatic hydrops caused by an abnormality in the absorption of endolymph at the endolymphatic sac remains the most promising theory to explain the symptoms of Ménière's disease. Other explanations for the cause of an endolymphatic hydrops, such as a hypoplasia of the vestibular aqueduct (Egami 1978; Yamamoto 1992), a genetic predisposition (Morrison 1995), or a viral aetiology (Vrabec 2003), have been suggested.

Currently no 'gold standard' diagnostic test for Ménière's disease exists. Diagnostic criteria vary among practitioners, who mostly diagnose Ménière's disease based upon the patient's history, neurotologic evaluation and clinical response to medical treatment. In 1972, the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) produced diagnostic guidelines (Alford 1972), which were revised in 1985 (Pearson 1985) and 1995 (Monsell 1995). According to these guidelines Ménière's disease is 'definite' when the last two spontaneous episodes of vertigo occur for at least 20 minutes, hearing loss of at least 20 decibels (dB) is objectified and tinnitus or aural fullness in the affected ear is experienced. Further investigation has to be performed to exclude any other disorder (Monsell 1995). When patients match the AAO-HNS criteria, but symptoms are secondary to a known cause, they are classified as having Ménière's syndrome.

A number of different treatment modalities have been identified for this disease, ranging from dietary measures (e.g. a low-salt diet) and medication (e.g. betahistine (Serc®), diuretics) to extensive surgery (e.g. endolymphatic sac surgery). Although a large number of studies have been conducted on therapy for Ménière's disease (see the Cochrane reviews of diuretics, betahistine and surgery: Burgess 2006; James 2001; Pullens 2013), an effective evidence-based therapy has never been established. Ménière's disease has a fluctuating natural course with remissions and exacerbations. Spontaneous remission is not uncommon, which makes evaluation of treatment difficult. The AAO-HNS therefore advises a follow-up period of at least two years to evaluate therapy (Coelho 2008; Durland 2005; Ghossaini 2006; Odkvist 2001).

Description of the intervention

Positive pressure therapy is a relatively new, minimally invasive method of treatment for Ménière's disease. In initial attempts to influence inner ear fluid pressure, a pressure chamber was used with the possibility of altering air pressure within a range of ± 110 cm H_2O (Ingelstedt 1976). Tjernstrom 1977 described the effects of positive pressure in the middle ear on the inner ear fluids and subsequently treated patients with Ménière's disease with overpressure in the middle ear. Densert et al presented a new method of local application of pressure in 1982, which was later developed in the Meniett® device (Densert 1982; Odkvist 2001).

The Meniett is a small, low-pressure generator that delivers a computer-controlled, complex algorithm of pulses at a frequency of 6 kHz for 0.6 seconds. After rising to a pressure level of 1.2 kPa, the pressure then oscillates between 0.4 and 1.2 kPa. In order to translate the pressure pulses to the middle ear (namely to the round window membrane), a ventilation tube has to be placed in the tympanic membrane, which requires a small surgical procedure. The device is portable and self administered, requiring a five-minute session three times each day, or more when vertigo exists. The Meniett device was approved by the US Food and Drug Administration for the treatment of Ménière's disease in 2002.

How the intervention might work

A number of animal studies have been undertaken to study the effect of middle ear pressure changes on inner ear pressure. Feijen et al monitored inner ear pressure in guinea pigs while applying pressure changes to the middle ear by using the Meniett 20® device in the outer ear canal (Feijen 2000). They found that middle ear pressure changes induced by the Meniett 20® were instantly transferred to the inner ear fluid. A single pressure pulse by the Meniett resulted in an increase of inner ear pressure and an 'undershoot' of pressure at the end of the pressure pulse, in which the inner ear pressure is lower than before application of the pressure pulse. In a number of seconds, inner ear pressure recovered to normal. In a follow-up study, different types of pressure pulses were used (Feijen 2002). When applying a constant increase in middle ear pressure, inner ear pressure increases accordingly, but immediately decreases to a new steady-state pressure (which is a little higher than the starting pressure) in a couple of seconds. When positive middle ear pressure ceases, inner ear pressure drops to negative and increases to normal in a couple of seconds.

In another animal study, Sakikawa et al demonstrated that appliance of pressure (49.2 cm H_2O) in the external ear canal

inhibited the formation of endolymphatic hydrops in guinea pigs after blockage of the endolymphatic duct (Sakikawa 1997).

Densert et al measured cochlear potential through electrocochleography while applying middle ear pressure pulses in a double-blind, placebo-controlled trial. In the placebo group no changes in electrocochlear parameters were found. In the active group, electrocochlear parameters indicated an improvement in inner ear electrophysiology (Densert 1997).

Several hypotheses have been proposed to account for the effects of pressure variations in the middle ear on the inner ear fluids. It has been suggested that pressure increase in the middle ear causes a decongestion of the labyrinthine vascular bed, improving endolymphatic drainage. Others propose that a pressure increase in the perilymphatic compartment influences the endolymphatic pressure. It is theorised that the energy of the pressure pulses displaces the perilymphatic fluid, which stimulates the flow of endolymphatic fluid either through the endolymphatic duct, or to the stria vascularis or surrounding tissues (Feijen 2000; Sakikawa 1997).

Why it is important to do this review

There is no real cure for Ménière's disease, although a number of different treatments exist. To our knowledge, no systematic review of positive pressure therapy has yet been conducted, while a number of randomised controlled trials have been carried out. A possible beneficial effect is suggested, but the extent of the effect is uncertain. A Cochrane review assessing the effects of positive pressure therapy in the treatment of Ménière's disease or syndrome is therefore warranted.

OBJECTIVES

To assess the effects of positive pressure therapy (e.g. the Meniett device) on the symptoms of Ménière's disease or syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Patients suffering from Ménière's disease not otherwise controlled by conservative therapy and without a history of surgical intervention. We graded as 'I' studies that had used the AAO-HNS criteria for Ménière's disease or syndrome, and which only included patients with 'definite' or 'certain' Ménière's disease. We graded as 'II' studies that included participants in which clear but less rigorous criteria were used. We graded as 'III' studies in which less clear criteria were used (AAO-HNS 1995; James 2001).

Types of interventions

Positive pressure therapy using the Meniett device or any other device or pressure chamber used to create overpressure in the middle or inner ear. This device should be compared with placebo, for example a sham device (a Meniett device which does not generate pressure pulses or an identical-looking device without pressure generation).

Types of outcome measures

Primary outcomes

- Control of vertigo or decrease in vertigo attacks

The AAO-HNS Committee on Hearing and Equilibrium proposed the "control of vertigo" as a main objective outcome measure when assessing therapy in Ménière's disease. The number of vertigo attacks in the interval between 18 and 24 months after treatment (y) is divided by the number of vertigo spells for the period of six months prior to the treatment (x) and multiplied by 100. The resulting number indicates the extent of "control of vertigo". The AAO-HNS further divides the control of vertigo (CoV) into classes, where Class A (CoV = 0) is complete control and class B (CoV 1 to 40) is substantial control. A minimum duration of follow-up of at least two years is advised by the AAO-HNS (AAO-HNS 1995).

We also considered studies with a shorter period of follow-up.

Secondary outcomes

- Loss or gain of hearing
- Severity of tinnitus
- Perception of aural fullness
- Functional level
- Complications and adverse events
- Sick days

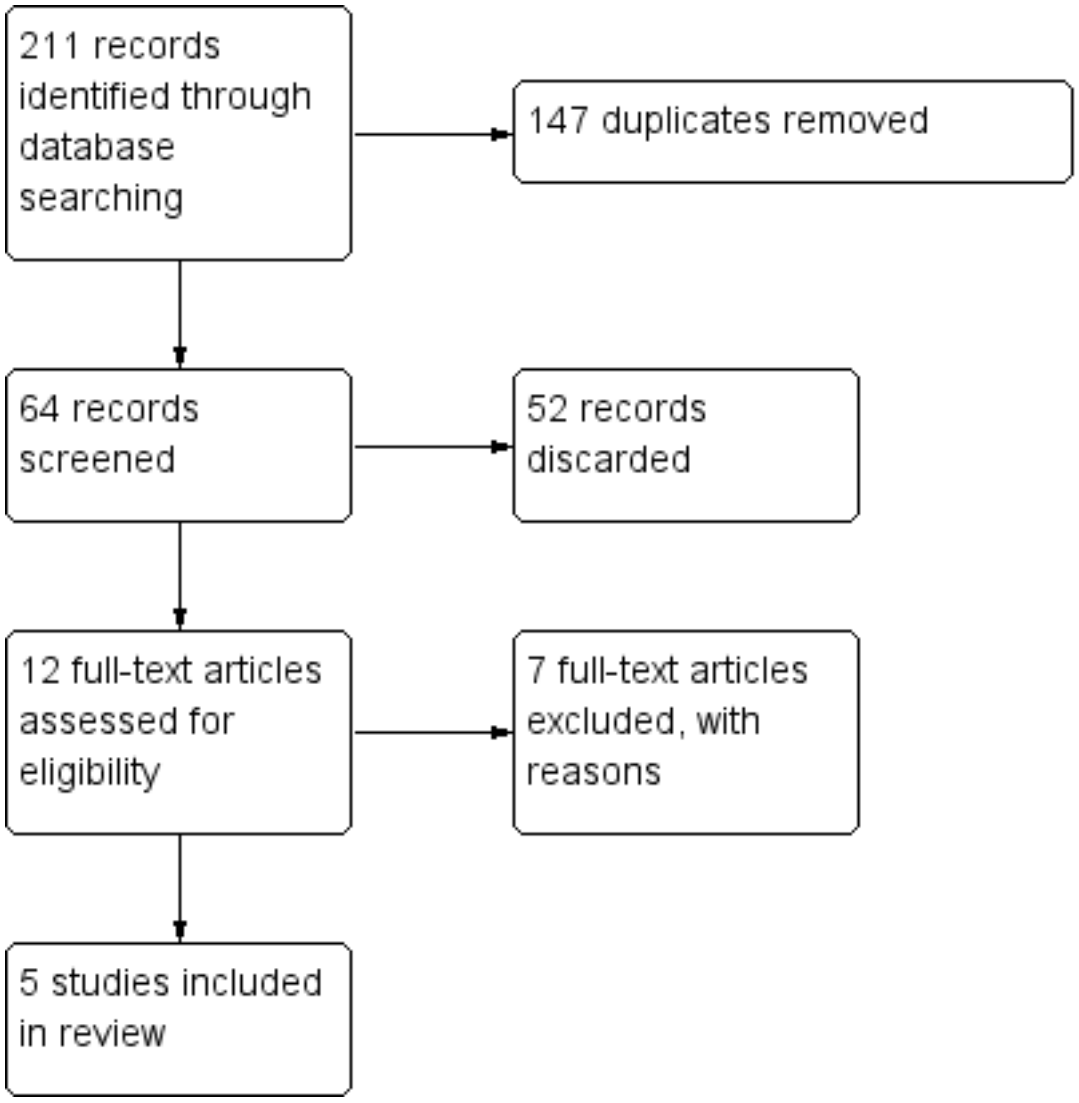
In the protocol we described 'quality of life' as a secondary outcome measure. In this review we have changed this to 'functional level', as this parameter is used in different studies and it is a derivate of everyday function and therefore quality of life. For the sake of clarity, the term functional level is used.

Additionally, we added 'sick days' as a secondary outcome because two studies included this measurement and because it is a complementary measurement of impairment due to Ménière's disease and can be related to quality of life.

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the latest search was 6 June 2014 (see Figure 1 for a flow chart of the search process).

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



Electronic searches

We searched the following databases from their inception for published, unpublished and ongoing trials: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 5); PubMed; EMBASE; CINAHL; AMED; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; ISRCTN; ClinicalTrials.gov; ICTRP; Google Scholar and Google. In searches prior to 2013, we also searched BIOSIS Previews 1926 to 2012.

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the*Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, 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 authors where necessary. In addition, we scanned the reference lists of a previous review on the subject and the review authors' own files for relevant studies. We handsearched conference proceedings for details of further trials and searched for unpublished trials by contacting the manufacturer (Medtronics).

Data collection and analysis

Selection of studies

Two authors scanned the initial search results to identify trials that loosely met the inclusion criteria. The two authors then independently used titles, keywords and (where available) abstracts of the identified citations to exclude trials that clearly did not meet the inclusion criteria for the review. If one of the authors concluded that the trial might possibly meet the criteria, we obtained the full paper for further study. Both authors assessed the hard copies of the articles passing this initial screening to

determine whether they met the inclusion criteria. We compared the results of the two independent selections. We resolved any disagreements by discussion.

Data extraction and management

The two authors independently extracted data from the studies using a standardised data extraction form. We additionally extracted the following data: AAO-HNS grade of diagnosis, type of device used, treatment protocol used (number of applications per day, total number of applications, duration of use of the device) and follow-up. There was no blinding of journal or author names and affiliations. Where necessary and where sufficient data from the study were not provided, we wrote to the authors of the study requesting further information.

Assessment of risk of bias in included studies

We assessed the quality of the selected studies using The Cochrane Collaboration's tool for assessing risk of bias. This tool addresses the following domains:

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel and outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting; and
6. other sources of bias.

Two authors judged each of these domains according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (see below): low, high and unclear (or uncertain) risk of bias. These results are presented in Figure 2 and Figure 3 and incorporated into the 'Risk of bias' tables using RevMan 5 (RevMan 2014). See Characteristics of included studies.

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

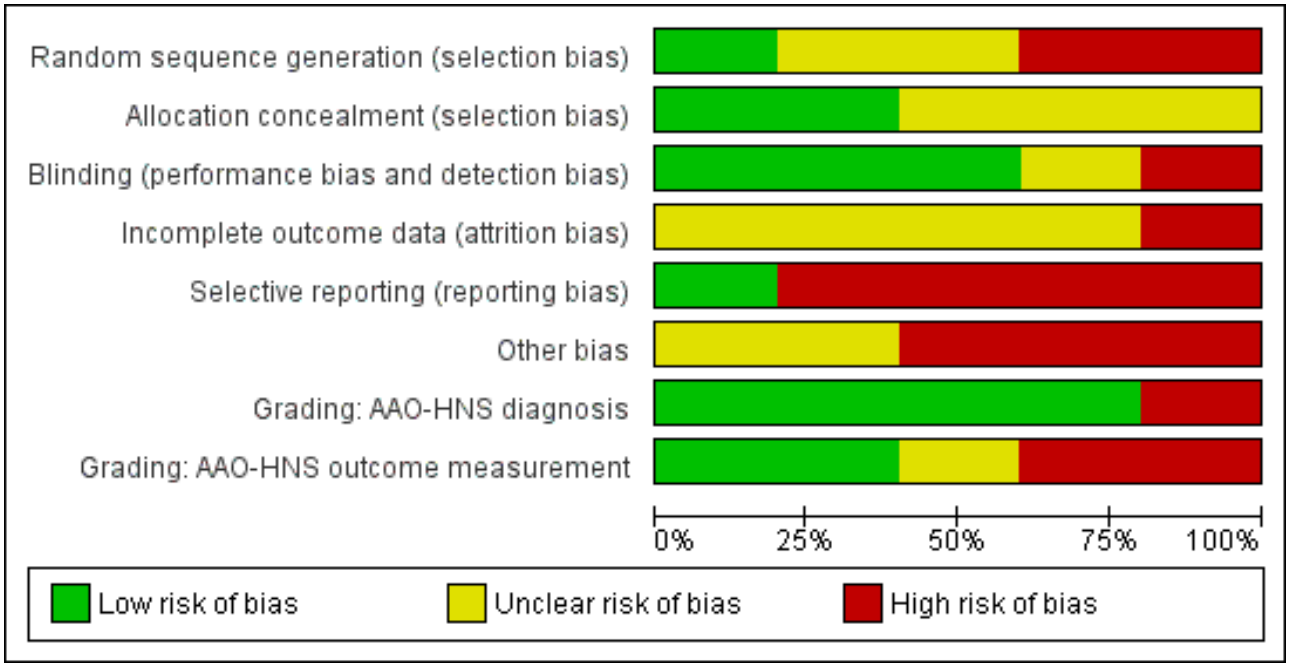
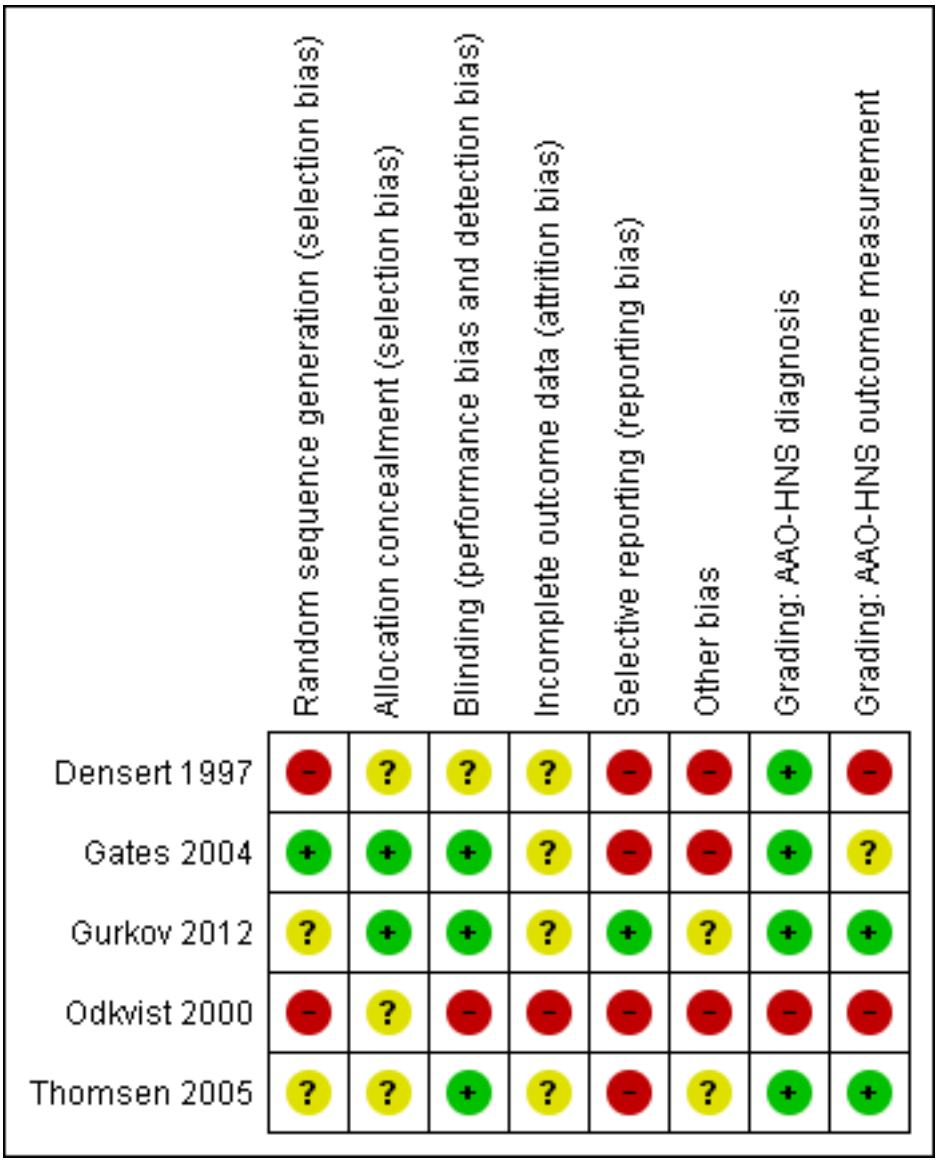


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



We also judged two extra domains: the certainty of the diagnosis of Ménière's disease (see also Types of participants) and the quality of outcome assessment (see Types of outcome measures). This is a modification of the 'Risk of bias' tool following an earlier Ménière's disease review by James and colleagues (James 2001).

The Cochrane Collaboration's tool for assessing risk of bias is described in Table 1 (Handbook 2011).

Dealing with missing data

When critical data were not reported in the included studies, we contacted the principal investigator and request the data. Dr Gurkov responded with additional data (Gurkov 2012). Additional data from Dr Gates are awaited (Gates 2004). The other authors were unreachable or did not respond to our request.

Assessment of heterogeneity

Where possible, we pooled study results using fixed-effect meta-analysis to calculate mean differences (MD). We tested statistical heterogeneity with both the I^2 statistic and the Chi^2 test. An I^2 value greater than 50% is considered to indicate substantial heterogeneity (Handbook 2011). If the I^2 value was 50% or less, we used a fixed-effect meta-analysis (Mantel 1959). If the I^2 value was greater than 50%, we explored the individual trial characteristics to identify potential sources of heterogeneity. We then performed meta-analysis using both fixed-effect and random-effects modelling (DerSimonian 1986), to assess sensitivity to the choice of modelling approach.

Assessment of reporting biases

We did not test for funnel plot asymmetry as there were fewer than 10 studies included in the meta-analysis (Handbook 2011).

Data synthesis

We planned that data analysis would be by intention-to-treat. In this review, for the primary outcome of control of vertigo or decrease in vertigo attacks the data were not compatible and of sufficient quality, therefore it was not possible to combine data in meta-analysis. For the secondary outcomes loss or gain of hearing and sick days, we pooled the results to present an overall estimate of the treatment effect. We used fixed-effect or random-effects meta-analysis depending on the degree of heterogeneity (see above).

Additionally we compared the duration of usage of the device and the duration of follow-up between all studies, but this was not used in any analysis.

Subgroup analysis and investigation of heterogeneity

A subgroup analysis comparing the type of overpressure device used (Meniett device, pressure chamber) was not possible due to heterogeneity between studies. We extracted subgroup data for the secondary outcome measures and tested for heterogeneity as described above.

Sensitivity analysis

As described above, due to clinical heterogeneity we only performed a meta-analysis for the secondary outcome measures. We had planned to use study quality in a sensitivity analysis had this been appropriate.

RESULTS

Description of studies

Results of the search

Our electronic database searches in June 2014 retrieved 211 initial results. After removal of duplicates and obviously irrelevant studies this number dropped to 64 reports. After the second selection, we removed 52 reports, either because they did not fit the inclusion criteria or because they were not RCTs. We retrieved 12 articles in full text. Of these, we excluded seven because they did not meet the inclusion criteria, did not compare positive pressure therapy with placebo or were not RCTs after further analysis (see Excluded studies and Characteristics of excluded studies for further details). Two articles were reviews and we scanned them for additional references, but found none. There are no ongoing studies or studies awaiting assessment.

We selected five studies for inclusion in the review (Densert 1997; Gates 2004; Gurkov 2012; Odkvist 2000; Thomsen 2005). This selection was made by two independent review authors (SvS and PPvB). A summary of the results of the search is presented in a flow diagram (Figure 1).

Included studies

See Characteristics of included studies.

Design

All five included studies were prospective, randomised and placebo-controlled.

Sample sizes

Study sample sizes ranged from 39 to 74. The total number of participants in the included studies was 265.

Setting

All studies were multicentre and took place at centres in Sweden, Denmark, Norway, Germany and the USA.

Participants

All five studies included patients with Ménière's disease.

The Densert 1997 study used the clinical criteria of the AAO-HNS 1995 Committee on Hearing and Equilibrium (Grade I). The inclusion criteria are: active clinical symptoms of Ménière's disease, cochlear hearing loss, aural pressure and recurrent spells of vertigo or dizziness six weeks prior to the intervention. The diagnosis of Ménière's disease was established at least one year but no longer than six years earlier: hearing loss was within the range of 20 dB to 65 dB pure-tone average, seven or more points on the Gibson's 10-point Ménière's scale (Gibson 1991; Appendix 3), electrocochleographic summated potential/action potential (SP/AP) ratio above 33%, age was 20 to 65 years and there was a patent ventilation tube in the tympanic membrane. All measurements, including electrocochleographic recordings, were performed before exposure to the active or placebo treatment, one week later in most patients. The patients who fulfilled the inclusion criteria were included in the study. Of these 39 participants, 21 were randomly assigned to active treatment and 18 to placebo. Demographic characteristics were not reported.

In the Gates 2004 study, the AAO-HNS criteria were not explicitly mentioned (Grade II). A total of 116 participants were contacted of whom 67 were eligible for inclusion and these were randomised for the study. The original sample size was 52, but an interim power analysis was performed halfway into the study, which suggested an increase in sample size by 10 patients. The active treatment group included 30 patients, with a mean age of 49.7 (range 34 to 67) and 67% were female. The placebo group contained 32 patients, with a mean age of 48.8 (range 36 to 71) and 69% were female. Both groups had a median duration of symptoms of 4.5 years (range two to seven years). Inclusion criteria were a clinical diagnosis of definite Ménière's disease, at least two vertigo attacks per month in the two months prior to the study and despite a low-sodium diet with or without diuretics for at least three months. Additional inclusion criteria were documented low-frequency sensorineural hearing loss and a history of fluctuating hearing, a functional level of 2 to 4, normal auditory brainstem responses and abnormal electrocochleography in the affected ear. Patients with 30% or greater canal weakness, measured with standard bithermal caloric tests, were excluded from randomisation.

In the Gurkov 2012 study, the AAO-HNS criteria were used for the diagnosis of Ménière's disease (Grade I). In total 154 patients met the inclusion criteria, but 74 patients were included. The power to detect a treatment effect was calculated as 80% (definite vertigo days, standard deviation (SD) = 5, difference in means = 3, n = 70). Demographic characteristics for included patients were provided. In the active group (n = 38) the mean age was 57 years (range 24 to 85), 19 patients were male and the mean duration of disease was 43 months. The placebo group patients (n = 36) had a mean age of 52 (range 19 to 74), 19 were male and the mean duration of disease was

57 months. To be included patients had to have had two or more episodes of vertigo lasting at least 20 minutes per month in the last two months and treatment with betahistine for three months.

In the Odkvist 2000 study, the AAO-HNS criteria are not described and patient characteristics are not given (Grade III). Fifty-six patients completed the study (n = 31 treatment, n = 25 control). Mean age, sex and duration of the disease are not reported; nor is the number of randomised patients or the power needed to detect a treatment effect. Inclusion criteria for this study were clinical and electrophysiological criteria for definite Ménière's disease, hearing impairment of 20 dB to 65 dB pure-tone average and "active vestibular symptoms close to the test".

Thomsen 2005 used the AAO-HNS criteria for the diagnosis of Ménière's disease (Grade I). A total of 63 patients met the first entry criteria, but 23 were later excluded. A total of 40 patients were included after the second entry and were used for analysis. The active treatment group contained 20 patients, aged between 26 and 69 years and with a duration of disease of between one and 36 months. The placebo group contained 20 patients, aged 20 to 61 and with a duration of disease of one to 20 months. According to the authors, both groups were identical in age, sex and duration of disease (although no exact data or analyses are available). Included patients required a diagnosis of Ménière's disease based on the AAO-HNS criteria, with a stage of 2 or 3, and a functional level of at least 3, hearing loss in the range of 20 dB to 65 dB pure-tone average in the frequencies 500 Hz, 1 kHz, 2 kHz and 3 kHz. Additionally, all patients needed a score of at least seven on the Gibson scale (Gibson 1991; Appendix 3), to be between 20 and 65 years of age and to have had at least eight vertigo attacks for at least 20 minutes during the previous year. For the second entry, after a period of two months monitoring, patients were only included with a minimum of two vertigo attacks lasting at least 20 minutes in the two months prior to and in the two months after ventilation tube placement.

Intervention

In the Densert 1997 study, a ventilation tube was inserted in all patients. A portable air pressure generator was used to deliver pressure changes within the range of 0 to 3 kPa. The generator was designed so that no negative pressure could be delivered. It is not specified which type of pressure generator was used. Measurements of the generator noise levels showed levels of 0 dB to 10 dB normalised hearing level for the active apparatus and 0 dB for the placebo device. The total amplitude of the pressure pulses was a maximum of 1.7 kPa, and the amplitude of the static pressure component was approximately two-thirds of the total amplitude. The frequency of modulation was 6 Hz and the duration of the pulse was 0.6 seconds with an interval of 4.4 seconds. The placebo device was an identical-looking pressure generator, displaying the same light patterns without pressure pulses. Exposure to pressure pulses was conducted for three minutes and repeated again for three more minutes after a one-minute period of refraction in between. Total time of exposure was at least six minutes. If patients reported an increase in aural fullness after the first three minutes of exposure, the pressure level was decreased to 1.0 kPa after a period of rest of approximately 20 minutes. Follow-up was immediate.

In the Gates 2004 study, a ventilation tube was placed in all patients followed by a two-week observation period (to rule out short-term effects of tube placement on symptoms). After two weeks, in the active treatment group the Meniett device was used to deliver 0.6 second pressure pulses at 6 Hz within the range of 0 to 20 cm H_2O to the ear. The five-minute treatment sequence had three cycles, each with one minute of pressure pulses and 40 seconds of pause. The placebo device was identical in appearance and produced a similar clicking sound and light display to the actual device during operation. The Meniett device and the placebo device were self administered three times daily. Follow-up assessments were scheduled monthly for a total period of four months. At the second and fourth visit, audiometry and electrocochleography were repeated. Additionally, participants were instructed to maintain a 1500 mg/day sodium diet. Participants were furthermore allowed to use their pre-study medication as needed.

Gurkov 2012 used a ventilation tube in all patients, with the Meniett device in the active group and a placebo device with identical acoustic properties to the Meniett device, which only produced a slight pressure increase of 2 cm H_2O. The Meniett device delivered 0.6 second pressure pulses at 6 Hz within a range of 0 to 20 cm H_2O to the ear canal. The five-minute treatment sequence had three cycles, each with one minute of pressure pulses and 40 seconds of no pressure pulses. The device was used three times daily (morning, afternoon and evening). All patients were first observed for four weeks before insertion of the ventilation tube. After insertion of the ventilation tube, all patients were observed again for four weeks. This was followed by a study period of 16 weeks, in which the active treatment group received low-pressure therapy and visited the study centre at four-week intervals. Patients were advised to continue their (pre-existing) daily dosis of betahistine of 48 to 72 mg/day. The study had a four-month follow-up period.

In the Odkvist 2000 study, a ventilation tube was inserted in the tympanic membrane in all patients, followed by a two-week observation period. Patients who fulfilled the inclusion criteria after this two-week period were included in the study. The active device (Meniett device) generated repeated pressure pulses in the middle ear, with pressure applications of the amplitude of 120 mm H_2O and consisted of complex pressure pulses and a 6 Hz sinusoidal modulation. The duration of each pulse was 0.6 seconds. The placebo device looked similar, but gave no stimulation to the ear. Duration and frequency of application was not described. Follow-up was after two weeks.

In the Thomsen 2005 study, a ventilation tube with a diameter of 1.25 mm was inserted through the tympanic membrane in all patients, followed by a two-month observation period. In the active treatment group, the Meniett device was used. Neither the frequency and duration of the pulses, nor the daily frequency were described in either group. The treatment period was two months, with follow-up at two, four and eight weeks. The placebo device was identical in appearance and produced a similar clicking sound and light display to the actual device during operation. The placebo device did not give any pressure pulse, except a slight pressure increase to 2 cm H_2O for five seconds to maintain the leakage test.

Outcome measures: primary outcome measures

Control of vertigo

In the Densert 1997 study, vertigo was measured with a visual analogue scale (VAS) as a secondary outcome measure. The VAS was not specified.

In the Gates 2004 study, participants scored their vertigo complaints daily on a four-point VAS on which 0 is a vertigo-free day and 4 is the worst vertigo attack ever experienced. A definitive vertigo day was any day with a vertigo score of 2, 3 or 4. Vertigo complaints were summarised in two ways: (1) vertigo severity, the monthly total of counted vertigo scores and (2) vertigo frequency, the proportion of counted vertigo days per time period. The proportion of sick days, days with an activity level of 3 or 4, was calculated over a period of four months.

In the Gurkov 2012 study, primary and secondary outcome measures are not specified. Vertigo was assessed using a five-point Likert scale. A vertigo-free day was scored as 0, days with mild attacks were scored as 1, moderately severe attacks lasting more than 20 minutes were scored as 2, severe attacks lasting an hour or more or accompanied by nausea or vomiting were scored as 3. A level 4 attack was the worst attack ever experienced to date. A definite vertigo day was any day with a vertigo score of 2 or more. For statistical analysis a vertigo score was used, which was a cumulative score over a period of four weeks. Additionally, sick days were defined as days with an activity score of 3 or 4.

In the Thomsen 2005 study, the frequency of vertigo attacks in the two months before the treatment period and in the last four weeks of the treatment period of four months was calculated. Additionally, the perception of vertigo was evaluated on a VAS in a daily diary. The VAS was not specified.

In the Odkvist 2000 study, primary and secondary outcome measures were not specified. Self reports (VAS) were used to assess vertigo and dizziness. This VAS was not specified.

Outcome measures: secondary outcome measures

Loss or gain of hearing

In the Densert 1997 study, hearing loss was not measured.

Gates 2004 measured the average low-frequency hearing thresholds (0.25 kHz, 0.5 kHz, 1 kHz) before the start of therapy and compared those with average thresholds at two and four months follow-up.

In the Gurkov 2012 study, pure-tone audiometry and air caloric irrigation testing were performed at every visit. The mean hearing threshold, assessed by pure-tone average at 0.25 kHz to 1 kHz was calculated.

In the Odkvist 2000 study, pure-tone audiometry was used to measure hearing loss at 500 kHz, 1000 kHz and 2000 Hz.

Thomsen 2005 stated that audiological evaluation occurred before and after the treatment period and the perception of hearing was analysed using a VAS.

Severity of tinnitus

Densert 1997 and Odkvist 2000 used a VAS to measure tinnitus.

In the studies of Gates 2004 and Gurkov 2012 tinnitus was not an outcome parameter.

Thomsen 2005 evaluated change in tinnitus on a VAS scale.

Perception of aural fullness

Densert 1997, Odkvist 2000 and Thomsen 2005 evaluated change in the perception of aural fullness on a VAS.

In the studies of Gates 2004 and Gurkov 2012, aural fullness was not an outcome parameter.

Functional level

In the protocol we described 'quality of life' as a secondary outcome measure. In this review we have changed this to 'functional level', as this parameter is used in different studies and it is a derivate of everyday function and therefore quality of life. For the sake of clarity, the term functional level is used. Quality of life was not used as an outcome measure in any of the included studies.

Activity level or functional level was not measured in the Densert 1997 study.

In the Gates 2004 study, activity level was scored using a 0 to 4 Likert scale: 0 indicated no reduction in activity; 1 and 2 indicated minor or moderate reductions in activity, respectively, without having to cancel a planned schedule; 3 indicated the need to stay at home, leave work or cancel a planned schedule; and 4 indicated being bedridden or largely incapacitated during the day. Use of the (symptom report) cards began before the initial clinical visit to record baseline symptom levels during the one-month pre-randomisation assessment period.

In the Gurkov 2012 study, activity level was scored using a 0 to 4 Likert scale: 0 indicated no reduction in activity; 1 and 2 indicated minor or moderate reductions in activity, respectively, without having to cancel a planned schedule; 3 indicated the need to stay at home, leave work or cancel a planned schedule; and 4 indicated being bedridden or largely incapacitated during the day. In this study, sick days were also registered as an activity score of 3 or 4.

Odkvist 2000 used a questionnaire to investigate the functional level in daily life and at work. This questionnaire is not further described.

Thomsen 2005 used the functionality profile suggested by the AAO-HNS (AAO-HNS 1995); this is a one- to six-point scale.

Adverse effects

Adverse effects were not noted by Densert 1997, Gates 2004 or Odkvist 2000.

In the Gurkov 2012 study, no adverse effects were noted. However, three participants were excluded, one because of treatment failure and two because of non-compliance. Another participant left without reason. There is no explanation of treatment failure or non-compliance. No adverse effects were reported, although one participant suffered from self limiting otitis media related to the ventilation tube.

In the Thomsen 2005 study, no adverse effects were noted but 23 participants were excluded from analysis because of non-compliance with the treatment or study protocol. It is unclear whether these participants had suffered from adverse effects because no explanation is given by the authors.

Sick days

In a change from protocol, we added 'sick days' as a secondary outcome because two studies included this measurement and because it is a complementary measurement of impairment due to Ménière's disease and can be related to quality of life.

In the Gates 2004 and Gurkov 2012 studies, sick days were described as days with an activity level of 3 or 4 (see above). Gates 2004 used the proportion of sick days for comparison across groups over a four-month period.

Other outcomes

Densert 1997 used the summated potential/action potential ratio of the electrocochleographic response complex as a primary outcome measure. A secondary outcome in this study was measurement of responses to low-frequency burst stimulation.

Gates 2004 compared the pretreatment electrocochleographic results between groups at two and four months follow-up.

Timing of outcome measurement

As stated in the protocol, we also considered studies with a shorter period of follow-up than that advised by the AAO-HNS (at least two years). There is only one study with a follow-up duration of two years (Gates 2006). This 2006 publication reports the longer-term follow-up of the participants reported by Gates 2004.

Excluded studies

All excluded studies were non-RCTs (Barbara 2001; Buchanan 2010; Densert 2001; Stokroos 2006), compared the Meniett with another pressure pulse generator (Franz 2005), or compared patients with Ménière's disease with delayed endolymphatic hydrops (Shojaku 2011; Watanabe 2011).

Risk of bias in included studies

Risk of bias in the included studies is summarised in Figure 2 and Figure 3 and detailed descriptions are given in the text below. Three out of five studies were at overall low risk (Gates 2004; Gurkov 2012; Thomsen 2005), the Densert 1997 study was at unclear risk and the Odkvist 2000 study was at high risk of bias.

Allocation

In the Densert 1997 study, no information is given about allocation sequence generation and concealment. There is also no information about the method of blinding. It is stated that patients in the placebo group received the same procedure, without stimulation of the ear. No power analysis was performed.

In the Gates 2004 study, the allocation sequence generation and concealment were adequate. All baseline characteristics between the active treatment group and the placebo group were comparable and no significant differences were reported between the two groups. Treatment group allocation was done using a randomised four-patient block design based on gender and normal/abnormal pretreatment caloric test results (abnormal being patients with a 30% or greater canal weakness). The rationale for this method of randomisation was not given. The original sample size was set at 52 patients, but an interim power analysis suggested the need to increase the number by at least 10. It is unclear why an interim power analysis was performed and it is unclear what clinical significant effect was used in this calculation.

In the Gurkov 2012 study, allocation sequence generation and concealment seemed adequate. All patients received a ventilation tube and it was stated that patients were randomly assigned to active treatment or placebo group. The method of randomisation was not described. Baseline characteristics of both groups were identical for age, sex, duration and severity of the disease and canal paresis. The power to detect a treatment difference was calculated as 80% (definite vertigo days, SD = 5, difference in means = 3, n = 70). A total of 74 patients were randomised, but six were later excluded. Excluded patients were only from the placebo group.

The Odkvist 2000 study was stated to be randomised, but no description is given of allocation sequence generation and concealment. It was stated that patients who were randomised to the placebo group received a similar-looking device and identical instructions. There was also no description of randomisation or whether the physicians were also blinded. No power analysis was performed.

In the Thomsen 2005 study, the allocation sequence generation and concealment are not adequately described. Only patients who had had at least two attacks in the two months before the pre-trial period and in the pre-trial period (after insertion of the ventilation tube) were included. In the actual trial they were randomised to active or placebo groups. The method of randomisation was not described. Baseline characteristics were identical in both groups for age, sex, length of history, severity of disease and degree of hearing loss. No power analysis was provided to account for the number of participants.

Blinding

In the Densert 1997 study, it is stated that both investigators and patients were blinded, but the methods of blinding are not described. The placebo was a device that looked similar, but which gave no stimulation to the ear. In all patients a ventilation tube was inserted and patients in the placebo group received the same procedure but without pressure stimulation.

In the Gates 2004 study, the participants and investigators were blinded to the treatment used. The active and placebo devices were identical in appearance and both generated a similar clicking sound and light display. The devices were sealed to assure integrity. It is not stated whether the placebo device gave a slight pressure pulse.

In the Gurkov 2012 study, it is stated that both participants and evaluators were blinded to the treatment assignments. The placebo device had identical acoustic properties to the Meniett device and produced only a slight pressure increase to 2 cm H_2O.

In the Odkvist 2000 study, it is stated that both investigators and patients were blinded, but the methods of blinding are not described. Placebo was applied by a device that looked similar, but did not give stimulation to the ear.

In the Thomsen 2005 study, it is stated that patients and investigators were blinded as to which type of apparatus was in use. The placebo device was visually identical to the active device but did not give any pressure pulses, except a slight pressure increase to 2 cm H_2O for five seconds to maintain the leakage test.

Incomplete outcome data

Densert 1997 gives no information about intention-to-treat analysis or loss of data. This study had an open design and it is not reported whether there were any excluded participants or drop-outs.

Gates 2004 reported an intention-to-treat analysis in the methods section of their article, stating that "data from participants failing before the end point were calculated as of their time of last follow-up and carried forward for the entire follow-up period". However, in the results section it is stated that two participants withdrew and three dropped out. The outcomes of these five patients were not carried forward to the endpoint. There were five treatment failures noted and, once again, it is stated that their data were carried forward to the endpoint, giving a total of 62 participant data sets to be evaluated. When the results are discussed, however, the total number of participants decreases over time (especially in the placebo group), resulting in a total of 57 participants at the four-month follow-up point. The reason for this is that data from failure cases were actually not included in the final analysis. This is a per-protocol analysis, not intention-to treat, contrary to what is claimed in the methods section. Furthermore, whether drop-outs and treatment failures were patients in the active treatment group or placebo is not described.

In the Gurkov 2012 study, 74 patients were randomised to active treatment or placebo. During follow-up there was one drop-out in the placebo group, with no reason given. In the Meniett group, five participants were excluded. In this group there was one drop-out, without explanation. Three participants left the treatment because of lack of improvement and one participant was excluded because of lack of compliance. No intention-to-treat analysis was performed.

In the Odkvist 2000 study, no information is given about intention-to-treat analysis or loss of data.

Thomsen 2005 stated that of the 63 participants who passed the entry criteria, 23 (36.5%) were later excluded because of "noncompliance with the treatment or study protocol." No further information on the reasons for exclusion was given. The number of excluded participants per treatment group was not given. No intention-to-treat analysis was performed.

Selective reporting

No information was given about missing data in the Densert 1997 and Odkvist 2000 studies (see above). The data for the participants who were considered failures are not given in Gates 2004, nor in Gurkov 2012.

In the Densert 1997 study, only mean scores and standard deviations are given for the electrocochleography results. For the measurements of vertigo, tinnitus and aural fulness no (statistical) data are provided.

The numerical data for the total monthly vertigo score (mean and standard deviation) are not given in the Gates 2004 study. Additionally, there are no numerical data, only proportions of days with vertigo, vertigo attacks and sick days. Without concrete mean and standard deviation data the results cannot be recalculated. The reason for using proportions is unclear.

Descriptions of mean scores and standard deviations are given in the Gurkov 2012 study.

In the Odkvist 2000 study, the numerical data for the total monthly vertigo score (mean and standard deviation) are not given. Only one table is presented without a proper scale for the measurements.

There are some questions regarding the statistical methods used when analysing the results. Thomsen 2005 described the methods of statistical analysis in detail, stating that the decrease in frequency of vertigo scores was recalculated in a ratio R (Ra or Rb) per treatment group. These ratios were compared to each other, giving a value T. A small T value indicates a beneficial effect of the A treatment compared to the B treatment. Strangely, when reviewing the results of the study, these T values are not given, but the results are given in means with standard deviations. The same goes for the visual analogue scale (VAS) score: a complex scoring system is described comparing individual VAS scores between patient A and patient B. The results of this scoring system are not given, however, as the results are given in means with standard deviations.

Other potential sources of bias

Follow-up

In the Densert 1997 study, there was only a direct evaluation after stimulation and no follow-up. There are no reports of participants lost to follow-up.

The loss to follow-up in Gates 2004 was 10 participants out of a total of 67 (14.9%). The reasons for the loss to follow-up are well described, although the number of failures is asymmetrically distributed (one in the active group and four in the placebo group).

The loss to follow-up over four weeks in the Gurkov 2012 study was two patients out of 74; four were excluded. The loss to follow-up (due to exclusion or drop-out) was asymmetrically distributed (five in the active group versus one in the placebo group). Sixty-eight participants were analysed (92%). A therapeutic effect of the slight pressure impulses of the placebo device cannot be excluded.

In the Odkvist 2000 study, no information was given about loss to follow-up after two weeks.

Follow-up was eight weeks in the Thomsen 2005 study. A large number of participants (36.5%) were excluded, without adequate descriptions.

Funding

No funding was declared by Densert 1997, Odkvist 2000 and Thomsen 2005.

The study Gates 2004 was funded by the Medtronic Xomed company in all participating centres. Dr Gates, the main author of the article, served as a paid consultant to Medtronic Xomed at a scientific retreat in 2000.

In the Gurkov 2012 study, no funding was declared. The Meniett devices were provided by Medtronic Xomed for the duration of the study.

Grading: AAO-HNS diagnosis

We graded all studies on a scale of I to III (for the grading system, see Types of participants). The Densert 1997 study used the clinical

criteria of the 1995 Committee on Hearing and Equilibrium and is therefore Grade I. Gurkov 2012 and Thomsen 2005 explicitly described the inclusion of patients with definite Ménière's disease using the AAO-HNS criteria, therefore these studies are also Grade I. Gates 2004 did not explicitly mention the AAO-HNS criteria, but the descriptions of the patients and symptoms are equal to the criteria, therefore it is also Grade I. In the Odkvist 2000 study, the AAO-HNS criteria are not mentioned and the article provides very few details about the inclusion criteria, therefore it is Grade III.

Grading: AAO-HNS outcome measurement

The AAO-HNS Committee on Hearing and Equilibrium describes clear measurement of 'control of vertigo'. The number of vertigo attacks in the interval between 18 to 24 months after treatment (y) is divided by the number of vertigo spells for the period of six months prior to the treatment (x) and multiplied by 100. The resulting number indicates the extent of 'control of vertigo'. None of the included studies used a follow-up period longer than four months, therefore none contain high-quality outcome measurements.

All studies used vertigo as a primary outcome measure but in different ways. Gates 2004 and Gurkov 2012 measured this in the same manner, by using a Likert scale of the severity of vertigo attacks (see also Types of outcome measures). Thomsen 2005 used the frequency of vertigo attacks and VAS scores. Densert 1997 and Odkvist 2000 only used VAS scores for measuring vertigo.

Effects of interventions

See: **Summary of findings for the main comparison** Positive pressure therapy versus placebo for Ménière's disease or syndrome

Positive pressure therapy versus placebo

Primary outcome

Control of vertigo or decrease in vertigo attacks

As all included studies used different measurements for vertigo, it was not possible to combine the data in a meta-analysis.

In the Densert 1997 study, no exact data are given, therefore this study cannot be used in any analysis. In this study, it was stated that subjective symptoms of vertigo, measured with visual analogue scales (VAS), did not significantly change in the active treatment group or in the placebo group. Transient aggravation of vertigo upon first use of the device was also not present. No exact data or statistical analyses are available in the article.

Gates 2004 used vertigo scores (see Included studies) at one, two, three and four months and the proportion of vertigo days in four months. The report describes a decrease in the total monthly definitive vertigo scores in the active group and in the control group. The results are given in a figure, which illustrates that the decrease in total monthly vertigo score is greater in the active group. No numerical data, means or standard deviations were given. The difference was greatest at the time points of one, two and three months and smallest at the four-month time point. According to the authors, an ANOVA repeated measures analysis with total definitive vertigo score as the dependent variable showed that the difference was significant (P value = 0.03), with treatment group and treatment months as the predictor variables. There was a decrease in the proportion of days with definite vertigo in both the placebo group and treatment group. This decrease was not significant at any time point and neither was the difference between groups at any time point. In the placebo group, the proportion of days with definitive vertigo decreased from a mean of 0.24 (standard deviation (SD) 0.22) at baseline to 0.11 (SD 0.16) after four months of follow-up. In the active group, the proportion of days with vertigo decreased from 0.20 (SD 0.17) at baseline to 0.10 (SD 0.14) after four months of follow-up. The mean difference between the groups after four weeks of treatment was -0.01 (95% confidence interval (CI) -0.08 to 0.06, overall effect Z = 0.26, P value = 0.79) (Analysis 1.1). With a multiple linear regression analysis of the cumulative four-month proportion of days with definite vertigo as a dependent variable and vertigo at baseline as predictor variable, significant results were found (coefficient 0.226, P value = 0.03).

In the Gurkov 2012 study, there was a significant decrease in cumulative vertigo scores over a four-month period in the active treatment group (pre- and post-treatment values 22.47 to 15.97) and the placebo group (20.42 to 19.23). The treatment effect (expressed as the difference between the pre-treatment and post-treatment vertigo score) was 6.5 for the active treatment group and 1.19 for the placebo group, which was significant (P value = 0.048). The mean difference (MD) for vertigo scores after four months in our analysis was -3.68 (95% CI -14.24 to 6.88) (Analysis 1.2). This is a non-significant difference (P value = 0.49). In the active treatment group there was a decline in vertigo scores in the first two months and a slight increase in the third month, followed by a decrease in the fourth month. In the placebo group, there was an increase in vertigo in the first month and in the fourth month. There are no statistical analyses available per month and no exact data are available over the different follow-up periods in the article, but Dr Gurkov provided us with raw data. There is also no explanation given by the authors for this attrition or the differences between the active and placebo groups. For vertigo days, no significant difference was found in the active group (6.5 to 4.08) or in the placebo group (5.94 to 5.52) (P value = 0.10). The mean difference (MD) between the groups was -1.55 (95% CI -5.40 to 2.30), which was not significant (P value = 0.43) (Analysis 1.3).

In Odkvist 2000, no exact data are given, therefore this study cannot be used in any analysis. In this study, the authors reported a significant improvement in vertigo scores in the active treatment group, established with visual analogue scales. There is no explanation available of the range of the scale, nor of the numbers in the figure, and no baseline figures or P values are reported. In the statistical analysis section, it is stated that student t-tests are used, but no exact data are described. Additionally, the meaning of the negative numbers in the placebo group is unclear: in the active group the score is 4.55, in the placebo group -0.64. We have not been able to recalculate this number due to a lack of statistical data.

Thomsen 2005 used the frequency of vertigo and VAS scores for vertigo, comparing the eight weeks before treatment to the last four weeks of treatment (a total of eight weeks of treatment). In this study, there was a decrease in the frequency of vertigo in the active group from 9.6 (6.7) in the eight weeks before treatment to 1.9 (4.1) in the last four weeks of treatment. The placebo group had a vertigo frequency of 10.5 (8.2) in the eight weeks before treatment compared to 4.0 (5.9) in the last four weeks of treatment (numbers given in mean (SD)). The difference in the frequency of vertigo between the four weeks before treatment compared to the last eight weeks of treatment was significantly decreased in both groups (although this was not mentioned in the article).

The MD in vertigo score in the last four weeks of treatment was -2.10 (95% CI -5.25 to 1.05) (Analysis 1.4). The difference *between* the two groups was not significant (P value = 0.19). There was a statistically significant decrease in total VAS score in both groups after treatment, with the greatest reduction in the treatment group. In the treatment group, VAS scores reduced from 67.3 (21.7) to 25.5 (20.5) and in the placebo group from 64.9 (22.4) to 46.6 (25.6) (P value = 0.005). The MD in our analysis was -21.10 (95% CI -35.47 to -6.73) (Analysis 1.5), with a significant overall effect favouring the Meniett group (P value = 0.004).

Secondary outcomes

Loss or gain of hearing

Pooled analysis of Gates 2004 and Gurkov 2012 showed a statistically significant hearing gain (MD 7.38 dB, 95% CI 2.51 to 12.25, overall effect P value = 0.003, Chi^2 = 0.10, df = 1 (P value = 0.76); I^2 = 0%) in favour of the placebo group compared to the Meniett group. We used a fixed-effect model (Analysis 1.6). The average low-frequency (0.25 kHz, 0.5 kHz, 1 kHz) pure-tone thresholds were lower in the placebo group compared to the active treatment group after treatment, meaning hearing improvement in the placebo group. Both studies combined showed a lower mean hearing threshold in the placebo group after treatment, but in the Gates 2004 study, there was an improvement in hearing found in both groups, while in the Gurkov 2012 study a slight deterioration in hearing levels was found.

Analysis per study

Gates 2004 described no change in hearing thresholds following treatment either within or between groups, but the mean low-frequency hearing thresholds in the active treatment group were 51.9 (23.4) and in the placebo group 42.7 (25.6).

Gurkov 2012 found a slight hearing loss in both groups. In the active treatment group the difference between pre- and post-treatment hearing thresholds increased from 53.18 to 49.15 dB at 1000 Hz and in the placebo group from 46.10 to 41.66 dB. These differences were not significant between groups (P value = 0.881).

In the Odkvist 2000 study, hearing improvement was found in some patients in the active treatment group, but not in the placebo group. The mean improvement was 4 dB for the 500 Hz, 5 dB for the 1000 Hz and 3 dB for the 2000 Hz frequency. Significant differences between pre- and post-treatment were found at the frequencies of 500 Hz (P value < 0.03) and 1000 Hz (P value < 0.01). The mean difference in hearing threshold levels pre- and post-treatment in the placebo group did not differ significantly at any frequency. No exact data are provided.

Thomsen 2005 stated that there was no difference in VAS perception of hearing between the study groups. No exact data are provided.

Severity of tinnitus

In the Odkvist 2000 study, results of measurements of tinnitus are given but without any explanation or standard deviations. A difference was shown between the active treatment group (2.52) and the placebo group (-1.6). The other studies either did not include tinnitus (Gates 2004; Gurkov 2012), or no exact data are given (Densert 1997; Thomsen 2005).

Perception of aural fullness

Aural fullness is not measured in the Gates 2004 and Gurkov 2012 studies and no exact data are given in the Densert 1997, Odkvist 2000 and Thomsen 2005 studies.

Functional level

Pooled meta-analysis for activity/functional level scores after treatment was not possible, due to the use of different measurements in the included studies.

Analysis per study

In the Gurkov 2012 study, the cumulative activity score decreased by 10.19 (SD 17.73) in the active treatment group and 4.45 (SD 15.8) in the placebo group. At the endpoint the activity score was 13.05 (SD 17.04) in the active treatment group and 20.23 (SD 25.44) in the placebo group. The treatment effect was not significantly greater in the active treatment group (P value = 0.08). There was no significant difference found between the two groups (z = 1.34, P value = 0.18) (Analysis 1.7).

In the Thomsen 2005 study, there was a decrease in functional level score in both groups when comparing pre- and post-treatment scores. This means better functional ability (i.e. less impairment). The decrease was significant in the treatment group (decrease from 4.2 to 2.4) compared to the placebo group (decrease from 4.1 to 3.5) (AAO-HNS criteria, one- to six-point scale: MD -1.10, 95% CI -1.81 to -0.39, z = 3.02, P value = 0.003) (Analysis 1.8).

In the Odkvist 2000 study, it was stated that the functionality profile changed in the active treatment group (3.48) versus the placebo group (-0.2), but no explanation of these numbers or standard deviations were given.

Complications and adverse events

None of the included studies reported complications or adverse events.

There were no reports of acute vertigo immediately after the first use of the device (Densert 1997), which can be interpreted as absence of (immediate) adverse events.

Sick days

Pooled analysis of sick days, measured in the Gates 2004 and Gurkov 2012 studies, did not show a statistically significant effect (MD -1.03, 95% CI -3.59 to 1.53, overall effect P value = 0.43 with Tau^2 = 2.77; Chi^2 = 4.28, df = 1 (P value = 0.04); I^2 = 77%). We used a random-effects model (Analysis 1.9).

Analysis per study

In the Gates 2004 study, there was a decrease in the proportion of sick days in both the placebo group and the active group. This decrease was not significant within groups or between groups at any time point. The proportion of sick days after four months of treatment was 0.01 (SD 0.02) in the active treatment group and 0.01 (SD 0.02) in the placebo group, with a mean difference of 0.00 (95% CI -0.01 to 0.01).

In the Gurkov 2012 study, the mean number of sick days decreased from 3.08 to 0.78 in the active treatment group and increased from 2.87 to 3.45 in the placebo group, with a significant treatment effect in the active treatment group (P value = 0.04). We calculated a mean

number of sick days in the intervention group of 0.76 (SD 1.61) and 3.45 (SD 7.09) in the placebo group after four months of treatment. The mean difference in our analysis was -2.69 (95% CI -5.24 to -0.14), favouring the Meniett (Analysis 1.9).

DISCUSSION

Summary of main results

There is no high-quality evidence of an effect of positive pressure therapy in Ménière's disease. No included studies specifically described the results of treatment in patients with Ménière's syndrome.

Although two of our included studies had an overall low risk of methodological bias (assessed using the Cochrane 'Risk of bias' tool), the lack of homogeneity in the outcome measures used made it inappropriate to combine results for our primary outcome, control of vertigo or decrease in vertigo attacks, in either a meta-analysis or sensitivity analysis. Vertigo frequency, vertigo scores after four months, vertigo days in four months and proportion of vertigo in four weeks did not show significant results (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4). Only one significant difference was found in one study, using visual analogue scale (VAS) scores for vertigo, favouring the Meniett® device (Thomsen 2005; Analysis 1.5). The clinical relevance of the results found is uncertain.

We carried out pooled meta-analyses for some of our secondary outcomes (loss or gain of hearing and sick days), which included two studies per analysis. We found significant results only for loss or gain of hearing (Analysis 1.6). The average low-frequency (0.25 kHz, 0.5 kHz, 1 kHz) pure-tone thresholds were lower in the placebo group compared to the active treatment group after treatment. This means that the hearing loss was greater in the Meniett group. However, when compared to baseline levels, one study found an overall increase of hearing level, while the other showed a slight deterioration of hearing levels.

It was not possible to use pooled data for the secondary outcome measure, functional level, due to heterogeneity in the outcome measures. One study did not show significant differences between the groups (Analysis 1.7). Only one included study showed a significantly lower functional level (less reduction in activities) in the Meniett group compared to the placebo group (Analysis 1.8). We found non-significant differences between the two groups in the number of sick days after treatment (Analysis 1.9).

No statistical data were available from the included studies for severity of tinnitus or perception of aural fullness.

No adverse effects or complications were reported in the included studies. It is stated that the Meniett device in itself is a minimally invasive device. However, a tympanostomy tube has to be inserted, with the associated risks of anaesthesia and the risks of (any) surgery such as infection and bleeding. A risk of otorrhoea and tympanosclerosis is also associated with the insertion of a tympanostomy tube.

In summary, there is insufficient good evidence of an effect of the Meniett device on vertigo. For the secondary outcome measures, we found inconclusive results for hearing loss and functional level. Hearing loss seems to be greater after using the Meniett compared to placebo. There is no evidence of improvement in vertigo, tinnitus, aural fullness or sick days.

Overall completeness and applicability of evidence

The evidence is currently insufficient to answer the review question: what are the effects of positive pressure therapy compared to placebo, in terms of vertigo, loss or gain of hearing, severity of tinnitus, severity of aural fullness, functional level and sick days in patients with Ménière's disease? We only included five studies in this review and we considered three of them to have an unclear or high risk of bias. Additionally, due to clinical diversity in the measurement of vertigo, it was not possible to perform a meta-analysis for this primary outcome measure. This limits the completeness of the evidence relevant to this review. The lack of sufficient high-quality evidence, and the absence of statistical meta-analysis for control of vertigo, makes it inappropriate to draw conclusions from the results regarding the applicability of positive pressure therapy for patients within the context of current practice in Ménière's disease.

Quality of the evidence

None of the five included studies used the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) criteria for 'control of vertigo'. Additionally, none of the studies use long-term follow-up as advised by the AAO-HNS.

Of the five included studies, we considered only three to have low risk of bias; the other two studies are at unclear and high risk of bias (Figure 2; Figure 3). All studies are reasonably consistent in their findings, showing only positive results for sub-analyses. No adverse effects were reported. Some comments can be made about the studies concerning the quality of the evidence (see also Summary of findings for the main comparison).

The Gates 2004 study is adequately set up with good allocation, blinding and randomisation. There are some questions, however, about the analysis of the results. First of all, the authors use a per-protocol analysis (while claiming to use an intention-to-treat analysis) when evaluating the efficacy of therapy. In doing so, we feel that the Gates 2004 study overestimates the effect of the placebo device (and underestimates the effect of the Meniett device), because most treatment failures dropped out of the placebo group. The decrease in days with vertigo is not significantly different in the treatment group compared to the placebo group in any of the follow-up months. A large number of statistical calculations are presented in this study (namely ANOVA) with a number of statistically significant outcomes. However, in our opinion, the most important and clinically relevant finding of this study is the fact that there is no statistical difference in the number of vertigo days between the two groups. Also, due to the summation of categorical variables, the results are unclear. There is no reported attempt to validate whether two days of grade 3 vertigo is clinically equivalent to three days with grade 2 vertigo. Additionally, participants had a low-sodium diet and a high proportion were using diuretics.

The Gurkov 2012 study is adequately set up with good allocation, blinding and randomisation. Selective reporting bias is unclear in the article, because all data are presented as mean difference, without exact means and standard deviations at each time point. However, Dr Gurkov supplied us with exact data for the study, allowing us to calculate means and standard deviations. Only the total vertigo score differed significantly between the active treatment and placebo group; definite vertigo days and vertigo-

free days did not differ between groups. Most drop-outs were in the placebo group, as in the Gates 2004 study. These drop-outs are not characterised and are left out of the statistical analysis, therefore there is no intention-to-treat-analysis. Although the study included four follow-up measurements, no differences between follow-up periods are presented. Additionally, there are no explanations given for the increase in vertigo scores after the third month of treatment in the active treatment group. In this study, betahistine was given additionally to the Meniett device. The authors concluded that a smaller overall treatment effect may be partially due to this additional treatment. We feel that the contribution of betahistine to the Meniett patients is unclear, as all patients were characterised as unresponsive to betahistine.

In the Thomsen 2005 study, the method of randomisation was not reported and only patients with at least two vertigo attacks in the two months after the insertion of a ventilation tube were selected. The study included somewhat non-transparent and complicated statistical results and was incompletely reported. Twenty-three patients were excluded because of non-compliance with the treatment or study protocol. There is no explanation of why these patients were non-compliant or to which group they were randomised. Due to this exclusion, no intention-to-treat analysis is possible. It is also unclear why the authors used the frequency of vertigo attacks in the two months before the insertion of the ventilation tube and not the frequency in the two months after the insertion of the ventilation tube, although it is stated that this is supposed to rule out the effect of the ventilation tube. A Monte Carlo statistical technique was used for analysis, although it is unclear why this technique was used. In this study, the vertigo attacks did not differ significantly between the active treatment group and the placebo group, but a significant improvement in VAS scores was found. It is not stated by the authors whether there was also a significant improvement in the placebo group following treatment.

For the studies of Densert 1997 and Odkvist 2000, inadequate or unclear description of allocation, blinding and randomisation, as well as unclear reporting bias affect the quality of their findings. However, these studies found similar results to the other studies.

Potential biases in the review process

We used an extensive search strategy, which included more than 14 databases and was subject to no language or publication restrictions, to capture all trials relevant to this review, both published and unpublished. It is unlikely that any relevant study has been missed in this review. We additionally scanned published reviews on positive pressure therapy for Ménière's disease (Medtronic ENT; NHS 2012), but did not find further references. We were able to contact the primary investigators of two included studies for additional data and information (Gates 2004; Gurkov 2012). We could not reach the other authors. We also contacted Medtronic for additional, ongoing studies, but have not received a reply.

We are not aware of any other potential biases in the review process.

Agreements and disagreements with other studies or reviews

A recent meta-analysis has described significant reductions in vertigo with the Meniett device (Ahsan 2013), which we cannot confirm in our review. For vertigo scores, the authors performed only qualitative analysis for individual studies. Taking in consideration the quality of the studies and the heterogeneity in the measurement of outcome measures in the different studies, we are more restrained in our conclusions compared to this review. As in our review, data for functional score could not be combined. No significant effects were found on pure-tone average (PTA) pre- and post-Meniett application. Additionally, we found significantly lower thresholds for hearing levels in the placebo group. Interestingly, Ashan et al also used prospective, retrospective and cross-sectional/unknown types of studies, which we did not include in our review. Additionally, we did not only investigate the results in the Meniett groups of the included studies, but compared these with the placebo groups for a more complete review.

A review of micro-pressure therapy for refractory Ménière's disease was performed by the UK National Institute of Health Research (NIHR) in April 2012 (NHS 2012). This review also included non-randomised clinical trials. Nevertheless, our findings are comparable with the conclusions described in this review. The same randomised controlled trials (RCTs) were included as in this review. Case series suggested positive results for vertigo, functionality profile and hearing. However, in the NIHR review two case series reported middle ear infections and immediate postoperative ear discharge in seven out of 74 patients, although the included RCTs did not report adverse effects or complications.

Medtronic has published an independent review of the Meniett pressure pulse generator and included the same RCTs as in this review (Medtronic ENT). Additionally, two case series studies and one retrospective study were also included. These three studies included a total of 59 patients. Their review suggested positive effects on vertigo, nausea and aural fullness, whereas tinnitus and hearing remained unchanged. In one study, two patients out of 10 had to be treated for otorrhoea.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to demonstrate the effectiveness of positive pressure therapy for the symptoms of Ménière's disease. No adverse effects were described in the included studies, although in other case series studies middle ear infections, immediate postoperative ear discharge or otorrhoea have been described.

The significant results found in this review should be considered inconclusive. Hearing loss overall seems to be greater after using the Meniett device compared to placebo, but separate analyses show opposing results. Analyses of functional level showed opposing results between studies, and neither definite vertigo scores or vertigo days, nor sick days improved.

Implications for research

In order to be able to achieve the primary objective of this review, to determine the effects of positive pressure therapy on the symptoms of Ménière's disease, compared with placebo,

further research is needed. Future randomised controlled trials should use the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) criteria for the diagnosis of Ménière's disease and control of the disease (Monsell 1995), use uniform criteria, adequately report study methods and statistics, and have a minimum follow-up period of two years.

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CHARACTERISTICS OF STUDIES

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

Densert 1997

Methods	**Allocation:** randomised, multicentre, placebo-controlled trial with immediate follow-up **Design:** placebo-controlled study
Participants	**Number:** n = 39 **Age/gender:** age 20 to 65 years old; sex distribution not described **Setting:** Department of Otolaryngology, University of Lund, Lund, Sweden and University Hospital, Linkoping, Sweden **Eligibility criteria:** duration of clinical symptoms of definite Ménière's disease according to the 1995 Committee criteria, such as cochlear hearing loss, aural pressure and recurrent spells of vertigo or dizziness within 6 weeks before the test, hearing loss within the range of 20 dB to 65 dB pure-tone average, 7 or more on the Gibson's 10-point Ménière's scale, ECoG recordings showing a SP/AP ratio of > 33%, age 20 to 65 years, a patent ventilation tube in the tympanic membrane **Exclusion criteria:** vestibular Ménière's disease, significant systemic disease requiring medication with steroids, or those receiving diuretics or vasodilators 2 weeks before the test and previous local overpressure treatment **Baseline characteristics:** only pre-ventilation tube values for ECoG measurements. In the active group: SP/AP (%) in 48.1 (11.6), W(ms) 2.8 (0.65) and for the placebo group: SP/AP (%) 44.6 99.6) and W(ms) 2.4 (0.7)
Interventions	**Intervention group:** portable air pressure generator **Comparator group:** placebo

Densert 1997 *(Continued)*

	Use of additional interventions: none
Outcomes	**Primary outcome:** ECoG measurements **Secondary outcomes:** VAS scores for vertigo, tinnitus, aural fullness
Notes	No use of Meniett device, but comparable air pressure generator

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Open study; no baseline characteristics of the included patients were given concerning vertigo, tinnitus or aural fullness
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether there are drop-outs or exclusions; no report or description of excluded patients
Selective reporting (reporting bias)	High risk	No exact data or statistical analysis given. Quote: "The results from the visual scales evaluating changes in the subjective symptoms on vertigo, tinnitus and aural fullness showed no significant changes in either the active or the placebo group"
Other bias	High risk	Overall lack of adequate description of the included patients, baseline characteristics and statistical data including lack of explanation of measurements in tables and figures
Grading: AAO-HNS diagnosis	Low risk	Grade 1
Grading: AAO-HNS outcome measurement	High risk	The AAO-HNS criteria for 'control of vertigo' are not used. There are no data on the frequency of vertigo. Additionally, there are no descriptions of the visual analogue scales used and no statistical presentations of the baseline characteristics or measurements after the experiment except for the ECoG measurements. The measurements are not according to the AAO-HNS criteria

Gates 2004

Methods	**Allocation:** prospective, randomised, double-blind, multicentre, placebo-controlled trial Follow-up after 1, 2, 3, 4 months **Design:** RCT
Participants	**Number:** n = 62 **Age/gender:** age 33 to 71 years, 67% female in the active group, 69% female in the placebo group **Setting:** 4 centres are involved: University of Washington, Seattle, Jacksonville Hearing and Balance Institute, Jacksonville, Duke University, Durham, NC and University of Michigan, Ann Arbor

Gates 2004 *(Continued)*

	Eligibility criteria: clinical diagnosis of active, definite, unilateral cochleovestibular Ménière's disease (Grade I) causing disruptive levels of vertigo (at least 2 attacks per month for the 2 months prior to the study), despite at least 3 months of treatment with a low-sodium diet, with or without diuretics. Additional entry criteria: documented low-frequency sensorineural hearing loss and a history of fluctuating hearing, functional level 2 to 4, normal auditory brainstem responses and an abnormal electrocochleogram in the affected ear **Exclusion criteria:** not described, but "3 participants were dropped because of protocol deviations: 1 because of a nonfunctioning tympanostomy and 2 because entry criteria were not satisfied; bilateral Ménière's disease and atypical labyrinthine disease" **Baseline characteristics:** in the active group: mean age 48.8 (9.1), left ear affected 56, canal weakness 34%, abnormal caloric test 53%, functional score 4, PTA threshold mean 51.5 (18.7), proportion of days with definite vertigo (median) 0.2 (0.15 to 0.29), proportion of sick days (median) 0.16 (0.05 to 0.29), diuretics use 81%. In the placebo group: mean age 49.7 (9.0), left ear affected 57, canal weakness 28.5%, abnormal caloric test 50%, functional score 4, PTA threshold 56.1 (19.7), proportion of days with definite vertigo (median) 0.2 (0.11 to 0.33), proportion of sick days (median) 0.13 (0.07 to 0.33), diuretics use 73%
Interventions	**Intervention group:** Meniett device **Comparator group:** placebo device **Use of additional interventions:** 1500 mg/day sodium diet. Additional (pre-study) medication allowed (including diuretics)
Outcomes	**Primary outcome:** vertigo: severity of vertigo and vertigo frequency **Secondary outcomes:** functional score, number of sick days, hearing loss
Notes	- Treatment duration: 4 months - Unclear whether the placebo device used slight pressure pulse generation - Observation period of 2 weeks after insertion of ventilation tube - Non-significant difference in vertigo symptoms before and after tympanostomy tube insertion - High rates of participants using diuretics - Addition low-sodium diet - Funded by Medtronic Xomed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No statistical difference in participant characteristics A randomised block design was used (balanced for every 4 participants), based on gender and normal/abnormal caloric test results
Allocation concealment (selection bias)	Low risk	Use of randomised block design; the Meniett manager received the assignments from the study monitor and both recorded the coded treatment assignment and device serial number
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated to be double-blind; both participants and evaluators were blinded. See also above
Incomplete outcome data (attrition bias)	Unclear risk	Flow chart and adequate description of drop-outs presented. The failures are asymmetrical; 9 in the placebo group and 3 in the active group. It is stated

Gates 2004 *(Continued)*

All outcomes		that there were no differences between these 12 participants in age, gender, vestibular function or baseline vertigo, but there are no statistical data available No intention-to treat-analysis
Selective reporting (reporting bias)	High risk	No adequate description and presentation of drop-outs (''..3 participants dropped-out because of protocol deviations; 1 because of a nonfunctioning tympanostomy tube and 2 because entry criteria were not satisfied on subsequent case review...") 2 withdrawals after 1 month and 5 treatment failures after 2 months were not adequately described ("...5 participants declared themselves as failures...")
Other bias	High risk	- The study is funded by Medtronic Xerox, the manufacturer of the Meniett device - The reason for the interim power analysis is unclear, as is the clinical significance on which the calculation was based - The effects of the additional low-sodium diet and medication cannot be ruled out completely
Grading: AAO-HNS diagnosis	Low risk	Grade 1
Grading: AAO-HNS outcome measurement	Unclear risk	The AAO-HNS criteria for 'control of vertigo' are not used. Instead of using the AAO-HNS calculation for vertigo attacks, a proportion of vertigo attacks is measured. Functional levels according to AAO-HNS criteria are used

Gurkov 2012

Methods	**Allocation:** prospective, randomised, double-blind, multicentre, placebo-controlled trial Follow-up after 4, 8, 12 and 16 weeks **Design:** RCT
Participants	**Number:** n = 74 **Age/gender:** age 19 to 74 years, 19 females in the active group (n = 38), 17 females in the placebo group (n = 36) **Setting:** 3 centres: Departments of Oto-Rhino-Laryngology, Head and Neck Surgery, Ludwig Maximilians University of Munich and Johann Wolfgang Goethe University of Frankfurt, Germany **Eligibility criteria:** diagnosis of definite Ménière's disease according to the AAO-HNS criteria (Grade I), including 2 or more definite, spontaneous episodes of vertigo of 20 minutes or longer, audiometrically documented hearing loss on at least 1 occasion, tinnitus or aural fullness in the treated ear and exclusion of other causes, 2 or more vertigo attacks per month in the last 2 months and treatment with betahistine for the last 3 months without subjective vertigo control **Exclusion criteria:** bilateral Ménière's disease, previous destructive or surgical therapy (e.g. gentamicin instillation or endolymphatic sac surgery) and age below 18 years **Baseline characteristics:** in the active group mean age 57, mean disease duration 43 months, Ménière's disease stage III and IV 19 and 5 participants, canal paresis 27.3%. In the placebo group mean age 52, mean disease duration 57 months, Ménière's disease stage III and IV 17 and 5 participants, canal paresis 29.1%

Gurkov 2012 *(Continued)*

Interventions	**Intervention group:** Meniett device **Comparator group:** placebo device **Use of additional interventions:** pre-existing medical therapy with daily doses of 48 mg to 72 mg of betahistine
Outcomes	**Primary outcome:** vertigo score, number of definite vertigo days and number of sick days **Secondary outcomes:** activity score, number of vertigo-free days, hearing threshold and caloric stimulus induced slow phase nystagmus velocity
Notes	- Treatment duration: 16 weeks - Comparison between 4 weeks before treatment and last 4 weeks of treatment - Placebo device used slight pressure pulse generation of 2 cm H_2O - Observation period of 1 month after insertion of ventilation tube - No funding, but the Meniett device was provided by Medtronic Xomed - Additional (pre-study) medication allowed of 48 to 72 mg/day betahistine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	154 patients met the inclusion criteria but 74 were accepted to participate in the study; unclear reasons for the non-participation of 80 patients
Allocation concealment (selection bias)	Low risk	Method of randomisation is not described ("... a total of 74 patients accepted, and were individually randomised into either the active treatment group or the placebo group..."). A 4-week observation period was used after insertion of the ventilation tube for all participants
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, adequately and explicitly described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Flow chart and description of drop-outs presented, but without adequate descriptions of drop-outs and treatment failure. No intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Adequate descriptions of methods and results at different follow-ups. Adequate presentation of data. No statistical analysis between follow-up periods, but authors supplied additional raw data on request
Other bias	Unclear risk	Use of slight pressure pulse of 2 cm H_2O in the placebo group; the possibility of a small therapeutic effect cannot be completely ruled out
Grading: AAO-HNS diagnosis	Low risk	Grade 1
Grading: AAO-HNS outcome measurement	Low risk	The AAO-HNS criteria for 'control of vertigo' are not used, but the frequency of vertigo is calculated using cumulative vertigo scores and number of vertigo days. Data from the 4-week interval before the treatment were compared with the 4-week period at the end of the 16-week treatment

Odkvist 2000

Methods	**Allocation:** prospective, randomised, double-blind, multicentre, placebo-controlled trial Follow-up after 2 weeks **Design:** RCT
Participants	**Number:** n = 56 **Age/gender:** age 20 to 65 years; sex distributed not described **Setting:** Department of Otolaryngology, University Hospital Linköping, Halmstad Hospital, Halmstad, Kalmar Hospital, Kalmar and Jöngköping Hospital, Jöngköping, Sweden **Eligibility criteria:** patients with definite Ménière's disease (Grade III), without any description of criteria used or characteristics **Exclusion criteria:** not described: "the patients who fulfilled the entry criteria were included in this study", without further explanation **Baseline characteristics:** no baseline characteristics were described
Interventions	**Intervention group:** Meniett device **Comparator group:** placebo device **Use of additional interventions:** unknown
Outcomes	**Primary outcome:** no statements made about primary and secondary outcome measures. The effects of overpressure treatment are estimated based on hearing function and subjective measurements on vertigo functionality profile and tinnitus **Secondary outcomes:** see above
Notes	- Treatment duration: 2 weeks - Use of placebo device with no pulse generation - No baseline characteristics are available nor clear description of the measurements - Unclear whether patients were allowed to use pre-study medication or continue a low-sodium diet

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods of randomisation not described. Patients who fulfilled the inclusion criteria after insertion of the ventilation tube were included. Baseline characteristics between groups not described
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blinding is not stated in the article. Blinding method is not adequately described. It is stated about the placebo device "...placebo was applied by a device that looked similar, but which gave no stimulation to the ear..."
Incomplete outcome data (attrition bias) All outcomes	High risk	No flow chart available; no description of drop-outs

Odkvist 2000 *(Continued)*

Selective reporting (reporting bias)	High risk	No baseline characteristics, only one figure without adequate legend or measurement scale. Very unclear presentation of data
Other bias	High risk	Student t-tests only, no Bonferroni correction for multiple testing
Grading: AAO-HNS diagnosis	High risk	Grade III
Grading: AAO-HNS outcome measurement	High risk	The AAO-HNS criteria are not used; unclear and insufficient description of the outcome measurements (including baseline characteristics and statistical data). Follow-up of two weeks was used

Thomsen 2005

Methods	**Allocation:** prospective, randomised, double-blind, multicentre, placebo-controlled trial Follow-up after 2, 4 and 8 weeks **Design:** RCT
Participants	**Number:** n = 40 **Age/gender:** age 20 to 65 years; no sex distribution is presented **Setting:** participating centres were 8 university hospitals in Sweden, Denmark and Norway and 2 regional hospitals in Sweden **Eligibility criteria:** diagnosis of definite Ménière's disease according to the AAO-HNS criteria (Grade I), with exclusion of cerebellopontine angle tumours or other intracranial disease using MRI, stage 2 or 3 of functional level according to the AAO-HNS criteria, hearing loss in the range of 20 dB to 65 dB, at least 7 on the Gibson 10-point score, between 20 and 65 years old and a history of at least 8 attacks of vertigo for at least 20 minutes during the previous year **Exclusion criteria:** previous surgery of the inner ear, any systemic disease requiring steroid therapy, use of diuretics or vasodilators within 2 weeks before entry into the study, bilateral disease or undergone any destructive procedure (e.g. injections with gentamicin). Suspected perilymphatic fistulae, patients with purely vestibular symptoms or those who were pregnant were also excluded **Baseline characteristics:** it is stated that the 2 groups were identical regarding age, sex, length of history, severity of disease and hearing loss (presented in figures, without exact data)
Interventions	**Intervention group:** Meniett device **Comparator group:** placebo device **Use of additional interventions:** not explicitly mentioned whether participants where allowed to use pre-existing medical treatment such as betahistine) or had a low-sodium diet
Outcomes	**Primary outcome:** change in frequency of vertigo, functionality profile and vertigo perception (VAS) **Secondary outcomes:** perception of tinnitus (VAS), perception of aural pressure (VAS), perception of hearing (VAS) and audiological evaluation of hearing
Notes	- Treatment duration: 2 months - Observation period of 2 months before insertion of ventilation tube - Observation period of 2 months after insertion of ventilation tube (entry 1). Only patients who maintained at least 2 attacks per month in this pre-trial entered the trial (entry 2)

Thomsen 2005 *(Continued)*

- Placebo device generated slight pressure pulses of 2 cm H_2O

- Unclear whether low-sodium diet and/or pre-study medication was allowed (except for diuretics and gentamicin injections)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation after 2-month pre-trial period, with selection of patients with at least 2 attacks in the 2 months before the trial and in the pre-trial (after insertion of the ventilation tube).Baseline characteristics presented, but without statistical analysis for differences between groups at baseline
Allocation concealment (selection bias)	Unclear risk	Adequate description of randomisation and allocation concealment is missing; "entry 2 represented randomization into either the placebo group or the active treatment group"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with adequate description of blinding. After a monitoring period and the first entry of patients, participants were randomised to the active treatment group or placebo. Quote: "...all decisions were taken before the code was broken..During the analysis, the statistician was blinded in the sense that the patients' treatments were described as A and B, with no information on which of the two groups was the actively treated group..."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description of exclusions/drop-outs, without explanation of the exclusion of 23 participants with non-compliance. No intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Differences at baseline present; significant changes at different follow-up periods with unclear description. Quote: "...functionality level improved statistically in the active group..and the same was the case for VAS evaluation of vertigo..", no description of the fact that the VAS evaluation was also significantly improved in the placebo group No description or analysis of drop-outs No numbers of included patients presented in the tables
Other bias	Unclear risk	Use of slight pressure pulse of 2 cm H_2O in placebo group
Grading: AAO-HNS diagnosis	Low risk	Grade I
Grading: AAO-HNS outcome measurement	Low risk	The AAO-HNS criteria for 'control of vertigo' are not used, but the frequency of vertigo attacks is compared between the 2 months prior to the insertion of the ventilation tube and the last 4 weeks of the 8-week treatment. Also, the AAO-HNS criteria for functional levels are calculated

AAO-HNS: American Academy of Otolaryngology - Head and Neck Surgery
ECoG: electrocochleography
MRI: magnetic resonance imaging
PTA: pure-tone average
RCT: randomised controlled trial
SP/AP ratio: summated potential/action potential ratio
VAS: visual analogue scale

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

Study	Reason for exclusion
Barbara 2001	Allocation: non-RCT
Buchanan 2010	Allocation: non-RCT
Densert 2001	Allocation: non-RCT
Franz 2005	Allocation: RCT Participants: patients with Ménière's disease Intervention: comparison of Meniett versus P-100 pulse generator
Shojaku 2011	Allocation: RCT Participants: comparison between patients with Ménière's disease and delayed endolymphatic hydrops
Stokroos 2006	Allocation: non-RCT
Watanabe 2011	Allocation: RCT Participants: comparison between patients with Ménière's disease and delayed endolymphatic hydrops

RCT: randomised controlled trial

DATA AND ANALYSES

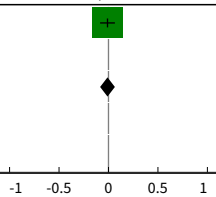
Comparison 1. Positive pressure therapy versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of days with vertigo in 4 weeks: vertigo scores > 2	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.08, 0.06]
2 Vertigo scores after 4 months	1	68	Mean Difference (IV, Fixed, 95% CI)	-3.68 [-14.24, 6.88]
3 Vertigo days in 4 months: vertigo scores > 2	1	68	Mean Difference (IV, Fixed, 95% CI)	-1.55 [-5.40, 2.30]
4 Vertigo frequency in the 8 weeks before and after 4 weeks of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.1 [-5.25, 1.05]
5 VAS scores for vertigo after 8 weeks of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-21.1 [-35.47, -6.73]
6 Loss or gain of hearing in 4 months (dB)	2	123	Mean Difference (IV, Random, 95% CI)	7.38 [2.51, 12.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Cumulative activity score at 4 months	1	68	Mean Difference (IV, Fixed, 95% CI)	-7.18 [-17.68, 3.32]
8 Change in functional profile between 8 weeks before and after 4 weeks of treatment	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.81, -0.39]
9 Sick days in 4 months	2	125	Mean Difference (IV, Random, 95% CI)	-1.03 [-3.59, 1.53]

Analysis 1.1. Comparison 1 Positive pressure therapy versus placebo, Outcome 1 Proportion of days with vertigo in 4 weeks: vertigo scores > 2.

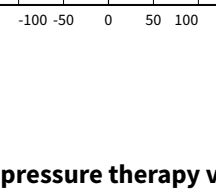
Study or subgroup	Meniett N	Meniett Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gates 2004	30	0.1 (0.1)	32	0.1 (0.2)		100%	-0.01[-0.08,0.06]
Total ***	**30**		**32**			**100%**	**-0.01[-0.08,0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.79)							



Favours Meniett — Favours placebo

Analysis 1.2. Comparison 1 Positive pressure therapy versus placebo, Outcome 2 Vertigo scores after 4 months.

Study or subgroup	Meniett N	Meniett Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gurkov 2012	37	15.6 (19.9)	31	19.2 (23.8)		100%	-3.68[-14.24,6.88]
Total ***	**37**		**31**			**100%**	**-3.68[-14.24,6.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.68(P=0.49)							



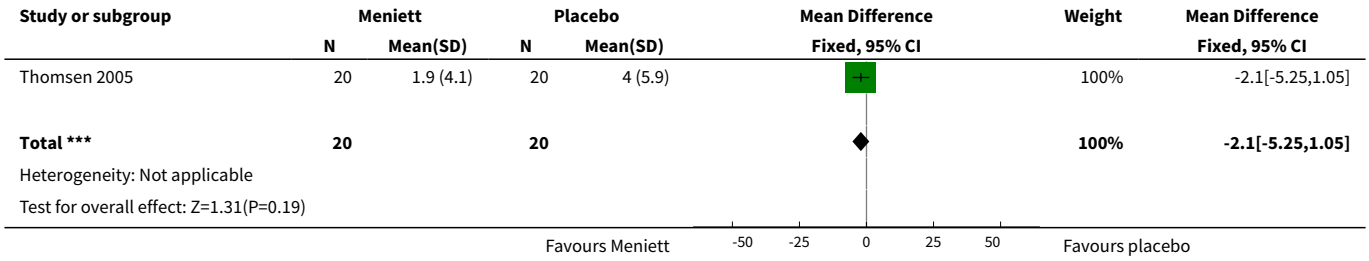
Favours Meniett — Favours placebo

Analysis 1.3. Comparison 1 Positive pressure therapy versus placebo, Outcome 3 Vertigo days in 4 months: vertigo scores > 2.

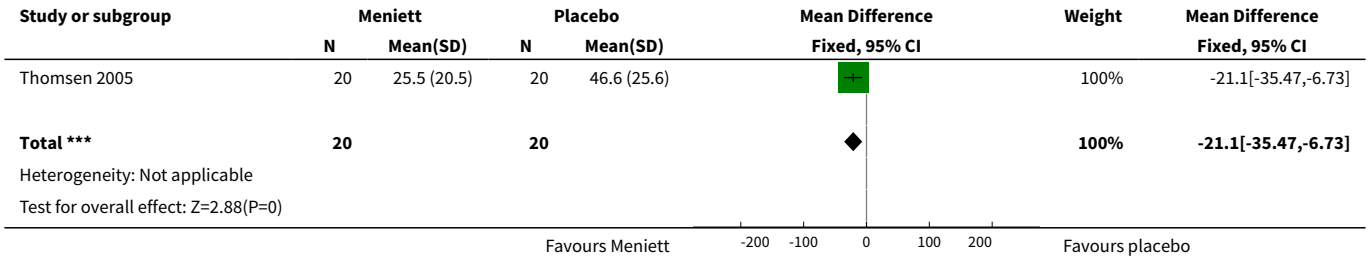
Study or subgroup	Meniett N	Meniett Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Gurkov 2012	37	4 (7.5)	31	5.5 (8.6)		100%	-1.55[-5.4,2.3]
Total ***	**37**		**31**			**100%**	**-1.55[-5.4,2.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.79(P=0.43)							

Favours Meniett — Favours placebo

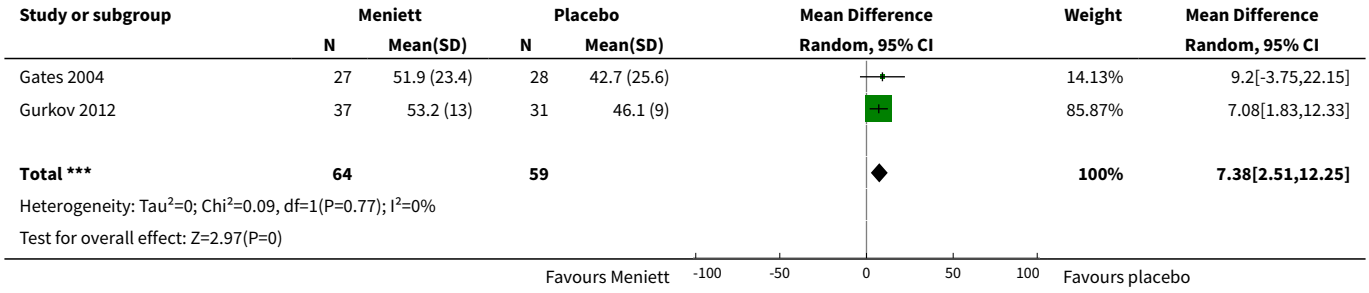
Analysis 1.4. Comparison 1 Positive pressure therapy versus placebo, Outcome 4 Vertigo frequency in the 8 weeks before and after 4 weeks of treatment.



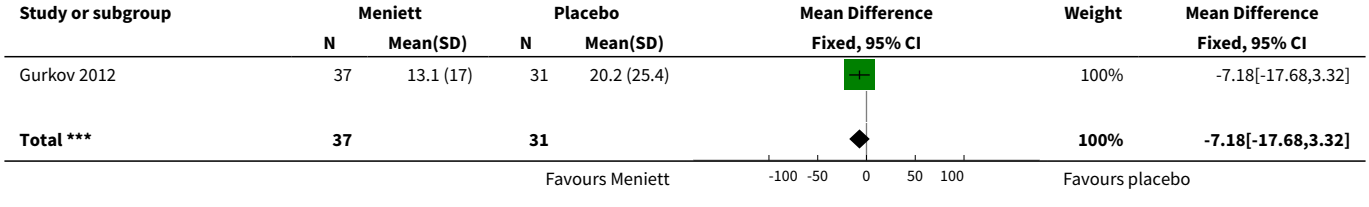
Analysis 1.5. Comparison 1 Positive pressure therapy versus placebo, Outcome 5 VAS scores for vertigo after 8 weeks of treatment.

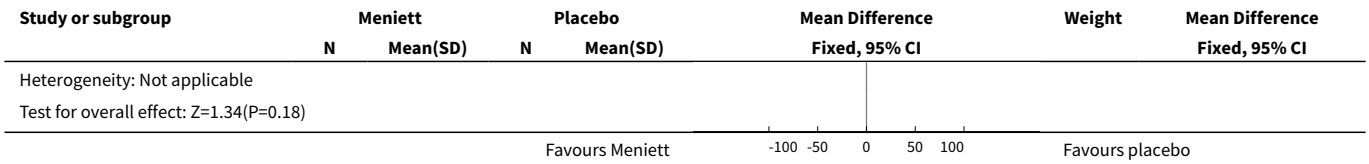


Analysis 1.6. Comparison 1 Positive pressure therapy versus placebo, Outcome 6 Loss or gain of hearing in 4 months (dB).

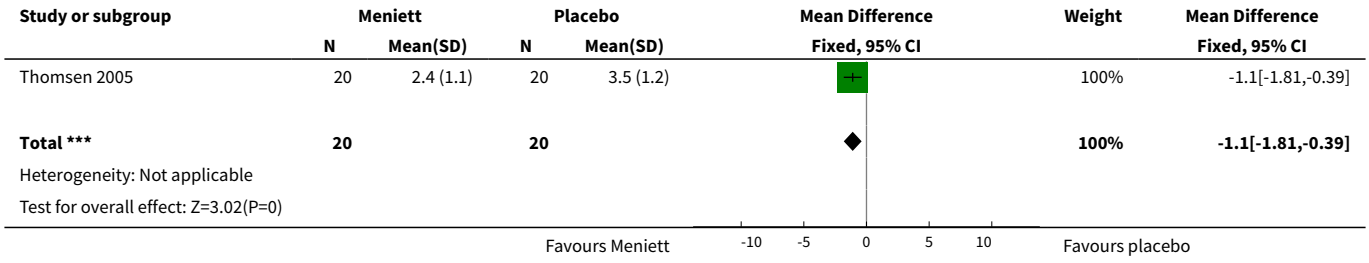


Analysis 1.7. Comparison 1 Positive pressure therapy versus placebo, Outcome 7 Cumulative activity score at 4 months.

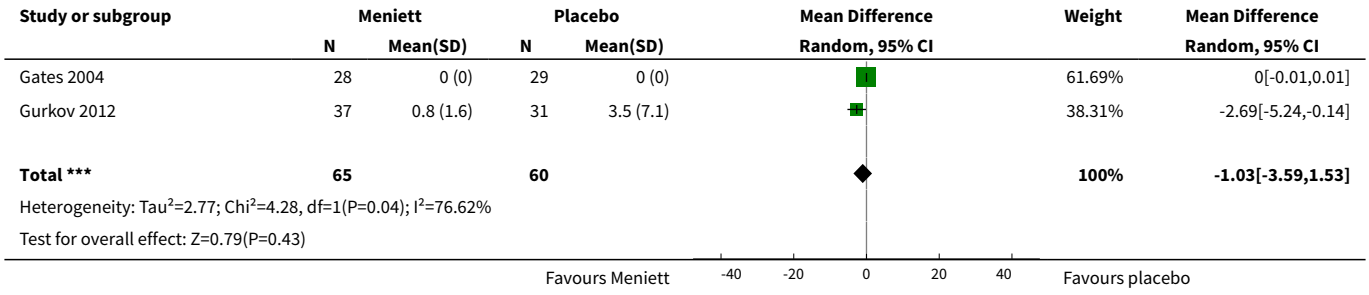




Analysis 1.8. Comparison 1 Positive pressure therapy versus placebo, Outcome 8 Change in functional profile between 8 weeks before and after 4 weeks of treatment.



Analysis 1.9. Comparison 1 Positive pressure therapy versus placebo, Outcome 9 Sick days in 4 months.



ADDITIONAL TABLES

Table 1. Cochrane 'Risk of bias' tool

Domain	Description	Review authors' judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Was knowledge of the allocated intervention adequately prevented during the study?

Table 1. Cochrane 'Risk of bias' tool *(Continued)*

Assessments should be made for each main outcome (or class of outcomes)		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors and what was found	Are reports of the study free of suggestion of selective outcome reporting?

APPENDICES

Appendix 1. Search strategy

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
#1 MeSH descriptor: [Endolymphatic Hydrops] explode all trees #2 meniere* or (endolymphatic and hydrops) or (labyrinth* and (hydrops or syndrome)) or (aural and vertigo) or (labyrinth* and vertigo) or (cochlea* and hydrops) #3 #1 or #2 #4 MeSH descriptor: [Pressure] explode all trees #5 meniett* or (pressure and treatment) or (pressure and therapy) #6 (puls* or pressure or overpressure or micropressure) and (instrument* or device* or apparatus or appliance* or equipment* or generat* or positive) #7 #4 or #5 or #6 #8 #3 and #7	#1 "Endolymphatic Hydrops" [Mesh] OR meniere* [tiab] OR (endolymphatic [tiab] AND hydrops [tiab]) OR (labyrinth* [tiab] AND (hydrops [tiab] OR syndrome [tiab])) OR (aural [tiab] AND vertigo [tiab]) OR (labyrinth* [tiab] AND vertigo [tiab]) OR (cochlea* [tiab] AND hydrops [tiab]) #2 meniett* [tiab] OR "Pressure" [Mesh] OR (pressure [tiab] AND treatment [tiab]) OR (pressure [tiab] AND therapy [tiab]) #3 (puls* [tiab] OR pressure [tiab] OR overpressure [tiab] OR micropressure [tiab]) AND (instrument* [tiab] OR device* [tiab] OR apparatus [tiab] OR appliance* [tiab] OR equipment* [tiab] OR generat* [tiab] OR positive [tiab]) #4 #1 AND (#2 OR #3)	1. MENIERE DISEASE/ 2. meniere*.tw. 3. ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).tw. 4. 1 or 3 or 2 5. meniett*.mp. 6. exp pressure/ 7. exp pulse generator/ 8. (puls* or pressure or overpressure or micropressure).mp. 9. (instrument* or device* or apparatus or appliance* or equipment or generat* or positive).mp. 10. 8 and 9 11. "pressure treatment".mp. 12. "pressure therapy".mp. 13. 5 or 6 or 7 or 10 or 11 or 12 14. 4 and 13	S1 (MH "Meniere's Disease") S2 TX meniere* or (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops) S3 S1 or S2 S4 meniett* S5 (MH "Pressure+") S6 puls* or pressure or overpressure or micropressure S7 instrument* or device* or apparatus or appliance* or equipment or generat* or positive S8 S6 and S7 S9 "pressure treatment" S10 "pressure therapy"

(Continued)

		S11 (S4 or S5 or S8 or S9 or S10) S12 S3 AND S11	
Cochrane ENT Disorders Group Trials Register (ProCite database)	**Web of Science (Web of Knowledge)**	**CAB Abstracts and AMED (Ovid)**	**ICTRP**
(meniere* OR (ENDOLYMPHATIC AND HYDROPS) OR (LABYRINTH AND HYDROPS) OR (LABYRINTH AND SYNDROME) OR (aural AND vertigo) OR (labyrinth AND vertigo) OR (cochlea AND hydrops)) AND (puls* OR pressure OR overpressure OR micropressure)	#1 Topic=((meniere* or (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops))) #2 Topic=((puls* or pressure or overpressure or micropressure) AND (instrument* or device* or apparatus or appliance* or equipment or generat* or positive)) #3 Topic=(MENIETT*) #4 Topic=("PRESSURE THERAPY") OR Topic=("PRESSURE TREATMENT") #5 #4 OR #3 OR #2 #6 #5 AND #1	1 (meniere* or (ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).mp. 2 meniett*.mp. 3 (puls* or pressure or overpressure or micropressure).mp. 4 (instrument* or device* or apparatus or appliance* or equipment or generat* or positive).mp. 5 3 and 4 6 (pressure and (treatment or therapy)).mp. 7 2 or 5 or 6 8 1 and 7	meniere* AND meniett OR meniere* AND pressure OR meniere* AND overpressure OR meniere* AND puls* OR meniere* AND micropressure*

Appendix 2. AAO-HNS guidelines for the diagnosis of Ménière's disease

AAO-HNS criteria for the diagnosis of Ménière's disease:

Vertigo

- Recurrent, well-defined episodes of spinning or rotation
- Duration ranging from 20 minutes to 24 hours
- Nystagmus associated with attacks
- Nausea and vomiting during vertigo spells common
- No neurological symptoms with vertigo

Deafness

- Hearing deficits fluctuate
- Sensorineural hearing loss
- Hearing loss progressive, usually unilateral

Tinnitus

- Variable, often low pitched and louder during attacks
- Usually unilateral on the affected side
- Subjective

Possible Ménière's disease

- Episodic vertigo of the Ménière's type without documented hearing loss or
- Sensorineural hearing loss, fluctuating or fixed, with dysequilibrium but without definitive episodes
- Other causes excluded

Probable Ménière's disease

- One definitive episode of vertigo

- Audiometrically documented hearing loss on at least one occasion
- Tinnitus or aural fullness in the treated ear
- Other causes excluded

Definite Ménière's disease

- Two or more definitive spontaneous episodes of vertigo of 20 minutes or longer
- Audiometrically documented hearing loss on at least one occasion
- Tinnitus or aural fullness in the treated ear
- Other cases excluded

Certain Ménière's disease

- Definite Meniere's disease, plus histopathologic confirmation

Stage of disease:

This is assessed by measuring pure-tone hearing threshold and is split into four stages:

- Stage I: a four-tone average of less than 26 dB
- Stage II: 26 to 40 dB
- Stage III: 41 to 70 dB
- Stage IV: more than 70 dB

Class of disease:

Frequency of vertigo spells over a six-month period:

- Class A: freedom from vertigo
- Class B: 1 to 40 vertigo spells
- Class C: 41 to 80 vertigo spells
- Class D: 81 to 120 vertigo spells
- Class E: more than 120 vertigo spells
- Class F: secondary treatment initiated due to disability from vertigo

Appendix 3. Gibson Ménière's scale

The Gibson 10-point Ménière's score can also be used to diagnose Ménière's disease. One point is awarded to each of 10 clinical signs. The closer the total score is to 10, the more likely the patient is to have the condition.

- Rotational vertigo
- Attacks of vertigo lasting more than 10 minutes
- Rotational vertigo associated with 1 or more of hearing loss, tinnitus or aural pressure
- Sensorineural hearing loss
- Fluctuating hearing loss
- Hearing loss or fluctuation associated with vertigo, tinnitus or aural pressure
- Peripheral tinnitus lasting more than 5 minutes
- Tinnitus fluctuating or changing with 1 or more of vertigo, hearing loss or aural pressure
- Aural pressure/fullness lasting more than 5 minutes
- Aural pressure fluctuating or changing with vertigo, hearing loss or tinnitus

Appendix 4. Activity score

- 0: no reduction in activity
- 1: minor or moderate reductions in activity, *without* having to cancel a planned schedule
- 2: minor or moderate reductions in activity, *with* having to cancel a planned schedule
- 3: need to stay at home, leave work or cancel a planned schedule
- 4: bedridden or largely incapacitated during that day

Appendix 5. AAO-HNS Ménière's disease functional level scale

Regarding your current state of overall functioning, not just during attacks, check the ONE that best applies:

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

CONTRIBUTIONS OF AUTHORS

Bas Pullens wrote the protocol. Peter Paul van Benthem revised the protocol and initiated the review. Sanne van Sonsbeek wrote the review, in accordance with Peter Paul van Benthem, who acted as co-writer.

DECLARATIONS OF INTEREST

Sanne van Sonsbeek: none known.
Bas Pullens: none known
Peter Paul van Benthem: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised the CENTRAL search strategy for added sensitivity.

In this review we changed 'quality of life' to 'functional level', as this parameter was used in some studies and is a derivate of everyday function and therefore quality of life. Quality of life was not a outcome measure used in any of the included studies. For the sake of clarity, only the term functional level is used. Additionally, we added 'sick days' as a secondary outcome because two studies included this measurement and because it is a complementary measure of impairment due to Ménière's disease and can be related to quality of life.

INDEX TERMS

Medical Subject Headings (MeSH)

Meniere Disease [*therapy]; Middle Ear Ventilation; Randomized Controlled Trials as Topic; Syndrome; Transtympanic Micropressure Treatment [instrumentation] [*methods]

MeSH check words

Humans