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Positive pressure therapy for Ménière's disease (Protocol).
Cochrane Database of Systematic Reviews 2021, Issue 12. Art. No.: CD015248.
DOI: 10.1002/14651858.CD015248.

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[Intervention Protocol]

Positive pressure therapy for Ménière's disease

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Editorial group: Cochrane ENT Group.
Publication status and date: New, published in Issue 12, 2021.

Citation: Webster KE, Harrington-Benton NA, Judd O, Kaski D, Maarsingh OR, MacKeith S, Ray J, Van Vugt VA, Burton MJ. Positive pressure therapy for Ménière's disease (Protocol). *Cochrane Database of Systematic Reviews* 2021, Issue 12. Art. No.: CD015248. DOI: 10.1002/14651858.CD015248.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of positive pressure therapy for Ménière's disease.

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BACKGROUND

Description of the condition

Ménière's disease was first described by Prosper Ménière in 1861 as a condition characterised by episodes of vertigo, associated with hearing loss and tinnitus (Baloh 2001). Sufferers may also report a feeling of fullness in the affected ear. Typically, it initially affects one ear, although some individuals may progress to develop bilateral disease. A hallmark of the condition is that symptoms are intermittent - occurring as discrete attacks that last from minutes to several hours, then resolve. However, over time there is usually a gradual deterioration in hearing, and there may be progressive loss of balance function, leading to chronic dizziness or vertigo.

The diagnosis of Ménière's disease is challenging, due to the episodic nature of the condition, clinical heterogeneity, and the lack of a 'gold standard' diagnostic test. Even the agreed, international classification system has scope for two categories of diagnosis – 'definite' and 'probable' (Lopez-Escamez 2015). In brief, a diagnosis of definite Ménière's disease requires at least two episodes of vertigo, each lasting 20 minutes to 12 hours, together with audiometrically confirmed hearing loss and fluctuating aural symptoms (reduction in hearing, tinnitus or fullness) in the affected ear. 'Probable' Ménière's disease includes similar features, but without the requirement for audiometry to diagnose hearing loss, and with scope for the vertigo episodes to last longer (up to 24 hours). Both categories ('definite' and 'probable') require that the symptoms are not more likely to be due to an alternative diagnosis, due to the recognised challenges in distinguishing between balance disorders.

Given the difficulties in diagnosis, the true incidence and prevalence of the disease are difficult to ascertain. A population-based study in the UK using general practice data estimated the incidence to be 13.1 per 100,000 person-years (Bruderer 2017), and the prevalence of the disease has been estimated at 190 per 100,000 people in the US (Harris 2010). It is a disorder of mid-life, with diagnosis typically occurring between the ages of 30 and 60 (Harcourt 2014). Some studies report a slight female preponderance, and there may be a familial association, with approximately 10% of patients reporting the presence of the disease in a first, second or third degree relative (Requena 2014).

The underlying cause of Ménière's disease is usually unknown. Ménière's disease has been associated with an increase in the volume of fluid in the inner ear (endolymphatic hydrops). This may be caused by the abnormal production or resorption of endolymph (Hallpike 1938; Yamakawa 1938). However, it is not clear whether this is the underlying cause of the condition, or merely associated with the disease. Some authors have proposed other underlying causes for Ménière's disease, including viral infections (Gacek 2009), allergic (Banks 2012) or autoimmune disease processes (Greco 2012). A genetic predisposition has also been noted (Chiarella 2015). Occasionally, the symptoms may be secondary to a known cause (such as a head injury or other inner ear disorder) – in these cases it may be referred to as Ménière's syndrome.

Although Ménière's disease is relatively uncommon, it has a profound impact on quality of life. The unpredictable, episodic nature of the condition and severe, disabling attacks of vertigo cause a huge amount of distress. Quality of life (including physical and psychosocial aspects) is significantly reduced for those with Ménière's disease (Söderman 2002). The costs of the condition are also considerable, both in relation to medical interventions (appointments, diagnostic tests and treatments) and loss of productivity or sick days for those affected by the condition (Tyrrell 2016).

Description of the intervention

A variety of different interventions have been proposed to treat people with Ménière's disease. These include dietary or lifestyle changes, oral treatments, treatments administered by injection into the ear (intratympanic) and surgical treatments. This review focuses on the use of positive pressure therapy to treat the symptoms of Ménière's disease.

Small pressure pulses are generated by a pump that is attached to tubing placed in the ear canal. Positive pressure therapy also requires the placement of a ventilation tube in the tympanic membrane, to encourage the pulsed pressure to transmit to the inner ear. The treatment is typically used for approximately five minutes at a time, and up to three times per day.

At present, there is no agreement on which is the ideal treatment for people with Ménière's disease – consequently there is no 'gold standard' treatment with which to compare this intervention.

How the intervention might work

As the underlying cause of Ménière's disease is poorly understood, so too are the ways in which the interventions may work.

Pressure changes in the middle ear can transmit to the inner ear through the round and oval windows. An increase in inner ear pressure has been suggested to result in decongestion of the inner ear vasculature, or to promote the opening of a temporarily blocked endolymphatic duct (Tjernström 1977). In this way, endolymph pressure is suggested to be altered. Intermittent positive pressure treatment was shown to reduce the development of endolymphatic hydrops in a guinea pig model (Sakikawa 1997).

Why it is important to do this review

Balance disorders can be difficult to diagnose and treat. There are few specific diagnostic tests, a variety of related disorders with similar symptoms, and a limited number of interventions that are known to be effective. To determine which topics within this area should be addressed with new or updated systematic reviews we conducted a scoping and prioritisation process, involving stakeholders (https://ent.cochrane.org/balance-disorders-ent). Ménière's disease was ranked as one of the highest priority topics during this process (along with vestibular migraine and persistent postural perceptual dizziness).

Although Ménière's disease is a relatively uncommon condition, the significant impact it has on quality of life demonstrates the clear importance of identifying effective interventions to alleviate the symptoms. There is considerable variation in the management of Ménière's disease on both a national and international scale, with a lack of consensus about appropriate first-line and subsequent therapies.

This review is part of a suite of six that consider different interventions for Ménière's disease. Through these reviews, we

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hope to provide a thorough summary of the efficacy (benefits and harms) of the different treatment options, to support people with Ménière's (and healthcare professionals) when making decisions about their care.

OBJECTIVES

To assess the benefits and harms of positive pressure therapy for Ménière's disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternate allocation, birth dates etc.).

Ménière's disease is known to fluctuate over time, which may mean that cross-over trials are not an appropriate study design for this condition. Cross-over RCTs will only be included if data can be extracted for the first phase of the study. If cluster-RCTs are identified then they will be eligible for inclusion, providing we can appropriately account for the clustering in the data analysis (according to methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2021).

We will include studies reported as full-text, those published as conference abstracts only and unpublished data.

Ménière's disease is characterised by episodic balance disturbance - the frequency of attacks may change over time (Huppert 2010). For studies to obtain accurate estimates of the effect of different interventions, we consider that follow-up of participants should be for at least three months - to ensure that participants are likely to have experienced a number of attacks during the follow-up period. Studies which followed up participants for fewer than three months will be excluded from the review.

Types of participants

We will include studies that recruited adult participants (aged 18 years or older) with a diagnosis of definite or probable Ménière's disease, according to the agreed criteria of the American Academy Otolaryngology - Head and Neck Surgery (AAO-HNS), the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology and the Bárány Society. These criteria include the following features:

Definite Ménière's disease:

- Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours.
- Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo.
- Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
- Not better accounted for by another vestibular diagnosis

Probable Ménière's disease:

- Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 24 hours.
- Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
- Not better accounted for by another vestibular diagnosis

If studies have used different criteria, we will include them if those criteria are clearly analogous to one of the above categories. For example, studies that have used earlier definitions of Ménière's disease (from the AAO-HNS guidelines of 1995) will also be included. If there is uncertainty over the criteria used for the study, we may contact the study authors for further information. If no additional information is available then a decision will be made on whether to include the study. This decision will be taken by authors who are masked to other features of the studies (such as study size, other aspects of methodology, results of the study) to avoid the introduction of bias in study selection.

We anticipate that most studies will include participants with active Ménière's disease. We will not exclude studies if the frequency of attacks at baseline is not reported or unclear, but we will highlight if there are differences between studies that may impact on our ability to pool the data, or affect the applicability of our findings.

We will exclude studies where participants have previously undergone destructive/ablative treatment for Ménière's disease in the affected ear (such as vestibular neurectomy, chemical or surgical labyrinthectomy), as they are unlikely to respond to interventions in the same way as those who have not undergone such treatment.

Types of interventions

We will include the following intervention:

- positive pressure therapy.

The main comparison will be:

- positive pressure therapy versus placebo/no treatment.

The use of positive pressure therapy requires the placement of a ventilation tube. However, this may be viewed as an 'active treatment' for Ménière's disease (see the companion review Webster 2021). We anticipate that some studies may use placement of a ventilation tube as the comparator arm for a study of positive pressure therapy. We will include these studies in the main analysis, but we will use subgroup analysis to determine whether the effect estimates are different between studies that use, or do not use, ventilation tubes in the comparator group.

Concurrent treatments

There will be no limits on the type of concurrent treatments used, providing these are used equally in each arm of the study. We will pool studies that include concurrent treatments with those where participants are not receiving concurrent treatment, but we will conduct subgroup analysis to determine whether the effect estimates may be different in those receiving additional treatment.

Types of outcome measures

We will assess outcomes at the following time points:

- 3 to < 6 months;

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- 6 to ≤ 12 months;
- > 12 months.

The exception will be for adverse event data, when we will use the longest time period of follow-up.

We searched the COMET database for existing core outcome sets of relevance to Ménière's disease and vertigo, but were unable to find any published core outcome sets. We therefore conducted a survey of individuals with experience of (or an interest in) balance disorders to help identify outcomes that should be prioritised. The results of this survey were used by the review author team to inform the choice of outcome measures in this review.

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes

- Improvement in vertigo
  - Measured as a dichotomous outcome (improved/not improved), according to self-report, or according to a change of a specified score (as described by the study authors) on a vertigo rating scale.
- Change in vertigo
  - Measured as a continuous outcome, to identify the extent of change in vertigo symptoms.
- Serious adverse events
  - Including any event that causes death, is life-threatening, requires hospitalisation, results in disability or permanent damage, or in congenital abnormality. Measured as the number of participants who experience at least one serious adverse event during the follow-up period.

Vertigo symptoms comprise a variety of different features, including frequency of episodes, duration of episodes and severity/intensity of the episodes. Where possible, we will include data for the vertigo outcomes that encompass all of these three aspects (frequency, duration and severity/intensity of symptoms). However, we anticipate that these data may not be available from all studies. If they are unavailable, then we will extract data on the frequency of vertigo episodes as an alternative measure for these outcomes.

Secondary outcomes

- Disease-specific health-related quality of life
  - Measured with the Dizziness Handicap Inventory (DHI, Jacobsen 1990), a validated measurement scale in widespread use. If data from the DHI are unavailable we will extract data from alternative validated measurement scales, according to the order of preference described in the list below (based on the validity of the scales for this outcome):
    - DHI short form (Tesio 1999);
    - DHI screening tool (Jacobsen 1998);
    - Vertigo Handicap Questionnaire (Yardley 1992a);
    - Meniere's Disease Patient Oriented Symptoms Inventory (MD POSI, Murphy 1999);
    - University of California Los Angeles Dizziness Questionnaire (UCLADQ, Honrubia 1996);
    - AAO-HNS Functional Living Scale (FLS, AAO-HNS 1995).
- Hearing
  - Measured with pure tone audiometry and reported as the change in pure tone average (PTA), or (alternatively) by patient report, if data from PTA are not available.
- Tinnitus
  - Measured using any validated, patient-reported questionnaire relating to the impact of tinnitus, for example the Tinnitus Handicap Inventory (THI, Newman 1996) or the Tinnitus Functional Index (TFI, Miekle 2012).
- Other adverse effects
  - Measured as the number of participants who experience at least one episode of the specified adverse events during the follow-up period. Including the following specified adverse effects:
    - otitis media;
    - persistent perforated tympanic membrane;
    - ear discharge;
    - ear pain;
    - new onset, permanent and total hearing loss in the affected ear;
    - new onset of tinnitus in the affected ear.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane ENT Trials Register (search via the Cochrane Register of Studies to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (search via the Cochrane Register of Studies to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to date);
- Ovid Embase (1974 to date);
- Web of Knowledge, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://trialsearch.who.int (search to date).

The subject strategies for databases will be modelled on the draft search strategy in Appendix 1. The strategy has been designed to identify all relevant studies for a suite of reviews on various interventions for Ménière's disease. Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1) (Lefebvre 2020).

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Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. In addition, the Information Specialist will run non-systematic searches of Google Scholar to identify trials not published in mainstream journals.

We will not perform a separate search for adverse effects. We will consider adverse effects described in included studies only.

Data collection and analysis

Selection of studies

We will consider using Cochrane's Screen4Me workflow to help assess the search results, depending on the number of results retrieved from the database searches. Screen4Me comprises three components:

1. Known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'a RCT' or as 'not a RCT'.
2. The machine learning classifier (RCT model) (Wallace 2017), available in the Cochrane Register of Studies (CRS-Web), which assigns a probability of being a true RCT (from 0 to 100) to each citation. For citations that are assigned a probability score below the cut-point at a recall of 99% we will assume these to be non-RCTs. For those that score on or above the cut-point we will either manually dual screen these results or send them to Cochrane Crowd for screening.
3. Cochrane Crowd is Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me website on the Cochrane Information Specialist's portal and see Marshall 2018, McDonald 2017, Noel-Storr 2018 and Thomas 2017.

At least two review authors will independently screen the remaining titles and abstracts using Covidence (https://www.covidence.org), to identify studies that may be relevant for this review. Any discrepancies will be resolved by consensus, or by retrieving the full text of the study for further assessment.

The full text for any study that may be relevant will be obtained, and will again be checked by two authors independently to determine whether it meets the inclusion criteria for the review. Any differences will be resolved by discussion and consensus, or through recourse to a third author if necessary.

Studies that are retrieved in full text but subsequently deemed to be inappropriate for the review (according to the inclusion/exclusion criteria) will be listed as excluded studies, according to the main reason for exclusion.

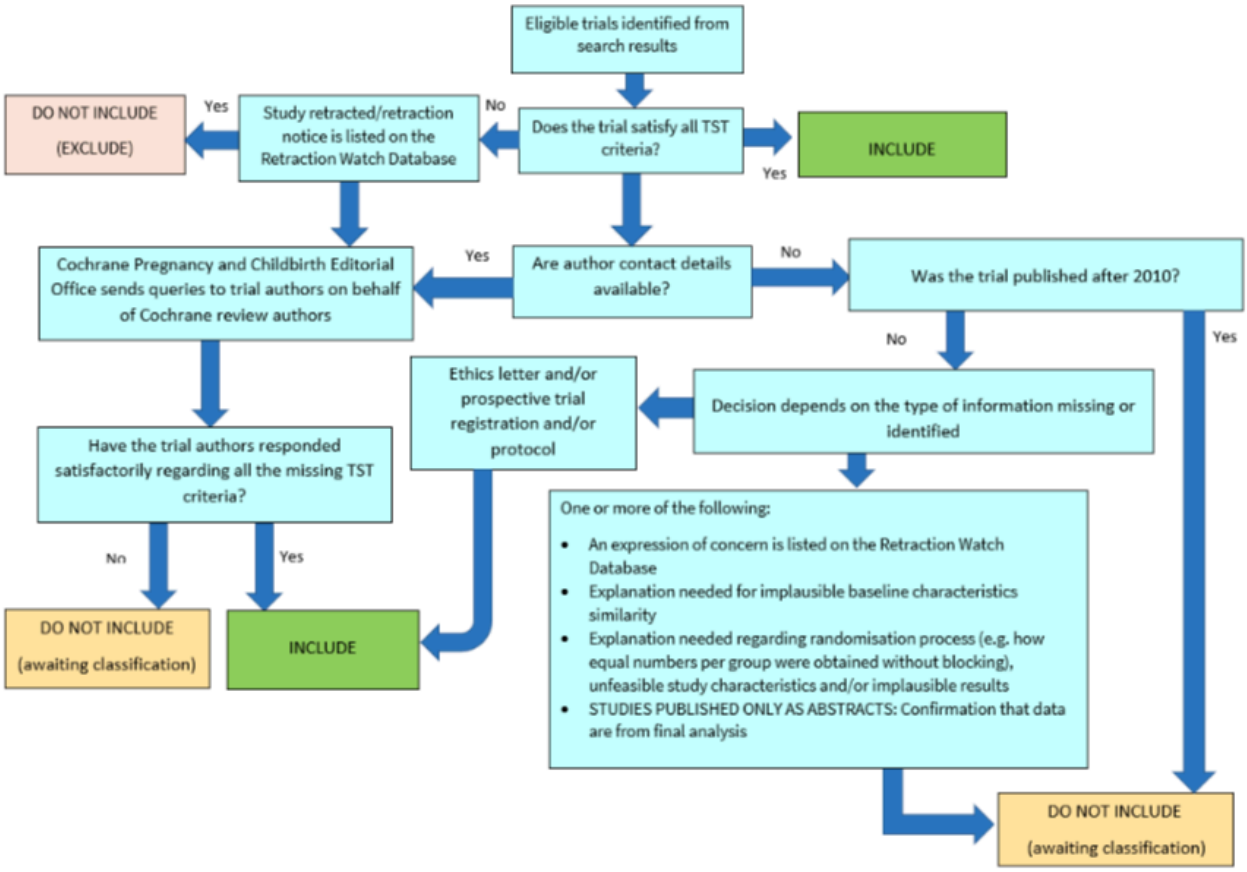
The unit of interest for the review is the study, therefore multiple papers or reports of a single study will be grouped together under a single reference identification. We will record the study selection process in sufficient detail to complete a PRISMA flow diagram and the 'Characteristics of excluded studies' table.

Screening eligible studies for trustworthiness

We will assess all studies meeting our inclusion criteria for trustworthiness using a screening tool developed by Cochrane Pregnancy and Childbirth. This tool includes specified criteria to identify studies that are considered sufficiently trustworthy to be included in the review (see Appendix 2). If any studies are assessed as being potentially 'high-risk', we will attempt to contact the study authors to obtain further information or address any concerns. If we are unable to contact the authors, or there is persisting uncertainty about the study then it will not be included in the main analyses of this review. The reasons for concern, and communication with the authors, will be described in full. The data from any studies where there are persisting concerns will be included only with a sensitivity analysis (see Sensitivity analysis). The process is outlined in Figure 1.

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Figure 1. The Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool



Data extraction and management

At least two review authors will independently extract outcome data from each study using a standardised data collection form. Where a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors will be checked against the original reports, and differences will be resolved through discussion and consensus, with recourse to a third author where necessary. If required, we will contact the study authors for clarification.

We will include key characteristics of the studies, including (as a minimum) the following information:

- study design, duration of the study, number of study centres and location, study setting and dates of the study;
- information on the participants, including the number randomised, those lost to follow-up or withdrawn, the number analysed, the age of participants, gender, severity of the condition, diagnostic criteria used, inclusion and exclusion criteria for the individual studies;
- details of the intervention, comparator and concomitant treatments or excluded medications;
- the outcomes specified and reported by the study authors, including the time points;
- funding for the study and any conflicts of interest for the study authors;
- information required to assess the risk of bias in the study, and to enable GRADE assessment of the evidence.

Once extracted data have been checked and any discrepancies have been resolved, the information will be transferred to Review Manager 5 (RevMan 2020) by a single author.

The primary effect of interest for this review will be the effect of treatment assignment (which reflects the outcomes of treatment for people who were assigned to the intervention) rather than a per protocol analysis (the outcomes of treatment only for those who completed the full course of treatment as planned). For the outcomes of interest in this review, we will extract the findings from the studies on an available case basis, i.e. all available data from all participants at each time point, based on the treatment to which they were randomised. This will be irrespective of compliance, or whether participants had received the intervention as planned.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract the following summary statistics for each trial and outcome:

- For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where change-from-baseline data are not available, we will extract the values for endpoint data instead. If values for the individual treatment

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groups are not reported, where possible we will extract summary statistics (e.g. mean difference) from the studies.

- For binary data: we will extract information on the number of participants experiencing an event, and the number of participants assessed at that time point. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. risk ratio) from the studies.
- For ordinal scale data: if the data appear to be normally distributed, or if the analysis performed by the investigators indicates that parametric tests are appropriate, then we will treat the outcome measure as continuous data. Alternatively, if data are available, we may convert these to binary data for analysis.
- For time-to-event data: we do not anticipate identifying any time-to-event data for the outcomes specified in the review. If these are identified then, where possible, we will extract data on hazard ratios from individual studies. If these data are not provided then we will extract alternative measures of treatment effect, such as the observed and expected number of events in each group, a P value and the number of events in each arm, or data from a Kaplan Meier curve.

If necessary, we will convert data found in the studies to a format appropriate for meta-analysis, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2021).

We have pre-specified time points of interest for the outcomes in this review. Where studies report data at multiple time points, we will take the longest available follow-up point within each of the specific time frames. For example, if a study reports an outcome at 12 weeks and 20 weeks of follow-up then we will include the 20-week data for the time point three to six months.

Assessment of risk of bias in included studies

Two authors will undertake assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

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

We will use the Cochrane risk of bias tool (Handbook 2011), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. serious adverse effects) as risk ratios (RR) with 95% confidence intervals (CIs). For the key outcomes that we will present in the summary of findings tables, we will also express the results as absolute numbers based on the pooled results and compared to the assumed risk. We may also calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk is typically either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium-risk population' or, alternatively, (b) the average risk of the control groups in the included studies is used as the 'study population' (Handbook 2021). If a large number of studies are available, and where appropriate, we may also present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we will express treatment effects as a mean difference (MD) with standard deviation (SD) or as a standardised mean difference (SMD) if different scales have been used to measure the same outcome. We will enter data presented as a scale with a consistent direction of effect. We will provide a clinical interpretation of the SMD values using either Cohen's d or by conversion to a recognised scale if possible.

Unit of analysis issues

Ménière's disease is unlikely to be a stable condition, and interventions may not have a temporary effect. If cross-over trials are identified then we plan to use only the data from the first phase of the study. If cluster-randomised trials are identified then we will ensure that analysis methods are used to account for clustering in the data (Handbook 2021).

If we identify studies with three or more arms, we will ensure these are included to avoid double-counting of any participants. If two arms relate to the same comparison (e.g. two different types of positive pressure therapy and placebo) then we will include these data by pooling the relevant intervention arms, or by splitting the shared placebo group between the two intervention arms (according to methods in the *Cochrane Handbook for Systematic Reviews of Interventions*; Handbook 2021).

Dealing with missing data

We will try to contact study authors via email whenever the outcome of interest is not reported, if the methods of the study suggest that the outcome had been measured. We will do the same if not all data required for meta-analysis have been reported (for example, standard deviations), unless we are able to calculate them from other data reported by the study authors.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining the included studies for potential differences between studies in the types of participants recruited, interventions or controls used and the outcomes measured. If necessary, we will provide a table to summarise the key similarities and differences between individual studies.

We will use the I^2 statistic to quantify inconsistency among the studies in each analysis. We will also consider the P value from the Chi^2 test. If we identify substantial heterogeneity, we will report this and explore possible causes through pre-specified subgroup analysis.

Assessment of reporting biases

We will assess reporting bias as within-study outcome reporting bias and between-study publication bias.

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Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol or trial registry, whenever this can be obtained. If the protocol or trial registry entry is not available, we will compare the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We will seek further information from the study authors. If no further information can be found, we will note this as being a 'high' risk of bias when the risk of bias tool is used. If there is insufficient information to judge the risk of bias we will note this as an 'unclear' risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We will assess funnel plots if sufficient studies (more than 10) are available for an outcome. If we observe asymmetry of the funnel plot, we will conduct more formal investigation using the methods proposed by Egger 1997. We will also report on whether there were any studies identified through trial registries and other sources (Searching other resources), with unpublished reports.

Data synthesis

Meta-analysis of numerical data

Where possible and appropriate (if participants, interventions, comparisons and outcomes are sufficiently similar in the trials identified) we will conduct a quantitative synthesis of results. We will conduct all meta-analyses using RevMan 2020. We anticipate that the underlying effect of the intervention may vary between studies, as there are likely to be differences between participants, settings and the interventions used for each study. We will therefore use a random-effects method for meta-analysis. We may explore whether the use of a fixed-effect model substantially alters the effect estimates, especially if few studies are included in the meta-analysis (see Sensitivity analysis).

For dichotomous data, we plan to analyse treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods.

For continuous outcomes, if all data are from the same scale, we will pool mean follow-up values with change-from-baseline data and report this as a mean difference. If there is a need to report standardised mean differences then endpoint and change-from-baseline data will not be pooled.

Improvement in vertigo symptoms may be assessed using a variety of methods, which consider different aspects of vertigo. These include:

- frequency of vertigo episodes;
- duration of vertigo episodes;
- severity/intensity of vertigo episodes;
- a composite measure of all of these aspects:
  - for example, assessed with a global score - such as "how troublesome are your vertigo symptoms?", rated on an ordinal scale.

For the outcomes "improvement in vertigo" and "change in vertigo", we will prioritise outcome measures that use a composite score - encompassing aspects of vertigo frequency, duration and severity/intensity. Examples of this may include a global rating scale of vertigo impact (rated from 0 to 10, where 0 is defined as no symptoms, and 10 is defined as the most troublesome symptoms) or the vertigo/balance subscale of the Vertigo Symptom Scale (Yardley 1992b), or Vertigo Symptom Scale Short Form (Yardley 1998). Where data from composite scores are not available, then we will include data on the frequency of vertigo episodes as an alternative measure.

Synthesis using other methods

If we are unable to pool numerical data in a meta-analysis for one or more outcomes we will provide a synthesis of the results using alternative methods, following the guidance in chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2021). The methods used will depend on the data available from the studies included in this review. We will provide descriptive statistics to summarise effect estimates if these are available from all studies. If effect estimates are not available, we may conduct vote counting, using the direction of effect. Where appropriate, we will present results using a visual display, such as an effect direction plot.

Subgroup analysis and investigation of heterogeneity

If statistical heterogeneity is identified for any comparisons, we will assess this considering the following subgroups:

- Different comparators
  - If studies have compared positive pressure therapy to no treatment, or to ventilation tubes alone, or to low pressure (placebo) treatment, we will investigate whether there are differences in the effect estimates for the different comparators.
- Different pressures/duration/frequency of administration.
  - If we identify differences in the methods of positive pressure administration that may result in heterogeneity we will investigate these with subgroup analysis according to the pressures used, duration and frequency of administration.
- Use of concomitant treatment.
  - We consider studies where all participants were using concomitant treatment separately from those where the intervention was exclusively used.
- Diagnosis of Ménière's disease
  - We will consider participants with 'definite' Ménière's disease separately from those with 'probable' Ménière's disease.

Where possible, if data are reported separately for subgroups within an individual study, we will extract and use these data for subgroup analysis. However, we anticipate that most subgroup analysis will need to be conducted at the level of the individual study. If more than 70% of participants in a study meet the criteria for a specific subgroup then the study will be included for the subgroup analysis.

We will use a formal test to assess whether subgroup differences may be present. However, these analyses are observational in nature, and therefore we will not draw conclusions about the relative effect of interventions for the different subgroups.

Sensitivity analysis

We intend to carry out sensitivity analyses for the primary outcomes only.

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If few studies are identified for meta-analysis, the random-effects model may provide an inaccurate measure of the between-studies variance. Therefore, we may explore the impact of using a fixed-effect model using a sensitivity analysis.

If there is uncertainty over the diagnostic criteria used for participants in the studies (for example, if it is not clear whether participants were diagnosed using criteria that are analogous to the AAO-HNS criteria) then we may also explore this by including/excluding those studies from the analysis.

The Pregnancy and Childbirth Group Screening Tool will be used to identify any studies where there are concerns over the data available. Any studies that are identified by this tool will be excluded from the main analyses in the review, but we will explore the impact of including the data from these studies through a sensitivity analysis.

We will also attempt to conduct a sensitivity analysis to exclude participants with 'probable' Ménière's disease from the main analysis, if sufficient data are available.

Summary of findings and assessment of the certainty of the evidence

Two independent authors will use the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (https://gradepro.org/) and the guidance in chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2021). Disagreements will be resolved through discussion and consensus, or with recourse to a third author if necessary. The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will justify all decisions to downgrade the certainty of the evidence using footnotes, and add comments to aid the interpretation of the findings, where necessary.

We will prepare a summary of findings table for the main comparison:

- positive pressure therapy versus placebo/no treatment.

We will include all primary outcomes in the summary of findings table. We will prioritise outcomes at the time point three to six months for presentation in the table.

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT, as well as an Evidence Synthesis Programme grant (NIHR132217). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

The development of the protocol (including the prioritisation of outcomes) for this review was informed by responses to a survey to encourage patient and public involvement in the review process. The development and distribution of this survey would not have been possible without the support of the Ménière's Society and the Migraine Trust, and the authors wish to thank them for their help.

The authors would like to thank Lee Yee Chong for her work on generic text that has been used and adapted (with permission) in the methods section of this protocol. We would also like to extend our thanks to Frances Kellie and Cochrane Pregnancy and Childbirth for their permission to use and reproduce the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool in this review.

The authors are grateful to Mr Malcolm Hilton for peer review of this protocol and the others in the Ménière's disease series, and to Anne Littlewood, Information Specialist with Cochrane Oral Health, for providing peer review comments on the draft search methods.

Many thanks, lastly, to Professor Peter Tugwell for the editorial sign-off of this protocol and the others in the series.

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APPENDICES

Appendix 1. Draft search strategies

This search strategy has been designed to identify all relevant studies for a suite of reviews on various interventions for Ménière's disease.

CENTRAL (CRS)	MEDLINE (Ovid)	Embase (Ovid)

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(Continued)

1 MESH DESCRIPTOR Endolymphatic Hydrops EXPLODE ALL AND CENTRAL:TARGET 155
2 (meniere*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 430
3 (endolymphatic near hydrops):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 35
4 (labyrinth* near hydrops):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 1
5 (labyrinth* near syndrome):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3
6 (aural near vertigo):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 15
7 (labyrinth* near vertigo):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 35
8 (cochlea near hydrops):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 0
9 (vestibular near hydrops):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 1
10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 AND CENTRAL:TARGET 469

1 exp Endolymphatic Hydrops/ 7701
2 "meniere*".ab,ti. 6321
3 (endolymphatic adj3 hydrops).ab,ti. 1636
4 (labyrinth* adj3 hydrops).ab,ti. 88
5 (labyrinth* adj3 syndrome).ab,ti. 49
6 (aural adj3 vertigo).ab,ti. 107
7 (labyrinth* adj3 vertigo).ab,ti. 133
8 (cochlea adj3 hydrops).ab,ti. 44
9 (vestibular adj3 hydrops).ab,ti. 102
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 9501
11 randomized controlled trial.pt. 542570
12 controlled clinical trial.pt. 94368
13 randomized.ab. 532663
14 placebo.ab. 221147
15 drug therapy.fs. 2368894
16 randomly.ab. 365180
17 trial.ab. 566659
18 groups.ab. 2242115
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 5107910
20 exp animals/ not humans.sh. 4881960
21 19 not 20 4442669
22 10 and 21 1798

1 exp Meniere disease/ 8470
2 "meniere*".ab,ti. 6547
3 (endolymphatic adj3 hydrops).ab,ti. 1886
4 (labyrinth* adj3 hydrops).ab,ti. 69
5 (labyrinth* adj3 syndrome).ab,ti. 40
6 (aural adj3 vertigo).ab,ti. 93
7 (labyrinth* adj3 vertigo).ab,ti. 116
8 (cochlea adj3 hydrops).ab,ti. 48
9 (vestibular adj3 hydrops).ab,ti. 110
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 9774
11 Randomized controlled trial/ 673476
12 Controlled clinical study/ 463803
13 Random$.ti,ab. 1700294
14 randomization/ 91705
15 intermethod comparison/ 274726
16 placebo.ti,ab. 328513
17 (compare or compared or comparison).ti. 545111
18 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 2359483
19 (open adj label).ti,ab. 90387
20 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 247761
21 double blind procedure/ 187174
22 parallel group$1.ti,ab. 28036
23 (crossover or cross over).ti,ab. 112372
24 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 361777
25 (assigned or allocated).ti,ab. 426550
26 (controlled adj7 (study or design or trial)).ti,ab. 386952
27 (volunteer or volunteers).ti,ab. 260161
28 human experiment/ 552250
29 trial.ti. 337746
30 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 5499535
31 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. 12240
32 comparative study/ or controlled study/ 8975971
33 randomi?ed controlled.ti,ab. 323613
34 randomly assigned.ti,ab. 143936
35 32 or 33 or 34 9160212
36 31 not 35 8708
37 Cross-sectional study/ 431819
38 randomized controlled trial/ or controlled clinical study/ or controlled study/ 8433754
39 (randomi?ed controlled or control group$1).ti,ab. 987184
40 38 or 39 8797325
41 37 not 40 281047
42 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 18859
43 (Systematic review not (trial or study)).ti. 184911
44 (nonrandom$ not random$).ti,ab. 17203
45 "Random field$".ti,ab. 2559
46 (random cluster adj3 sampl$).ti,ab. 1380
47 (review.ab. and review.pt.) not trial.ti. 920756
48 "we searched".ab. 61866
49 review.ti. or review.pt. 3115434
50 48 and 49 38137
51 "update review".ab. 117
52 (databases adj4 searched).ab. 44953
53 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cat-

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(Continued)

	tle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 1119864
	54 36 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 50 or 51 or 52 1375407
	55 30 not 54 5217196
	56 10 and 55 1254

Appendix 2. Trustworthiness Screening Tool

This screening tool has been developed by Cochrane Pregnancy and Childbirth. It includes a set of predefined criteria to select studies that, based on available information, are deemed to be sufficiently trustworthy to be included in the analysis. These criteria are:

Research governance

- Are there any retraction notices or expressions of concern listed on the Retraction Watch Database relating to this study?
- Was the study prospectively registered (for those studies published after 2010)? If not, was there a plausible reason?
- When requested, did the trial authors provide/share the protocol and/or ethics approval letter?
- Did the trial authors engage in communication with the Cochrane Review authors within the agreed timelines?
- Did the trial authors provide IPD data upon request? If not, was there a plausible reason?

Baseline characteristics

- Is the study free from characteristics of the study participants that appear too similar (e.g. distribution of the mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017)?

Feasibility

- Is the study free from characteristics that could be implausible? (e.g. large numbers of women with a rare condition (such as severe cholestasis in pregnancy) recruited within 12 months);
- In cases with (close to) zero losses to follow-up, is there a plausible explanation?

Results

- Is the study free from results that could be implausible? (e.g. massive risk reduction for main outcomes with small sample size)?
- Do the numbers randomised to each group suggest that adequate randomisation methods were used (e.g. is the study free from issues such as unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, if the authors say 'no blocking was used' but still end up with equal numbers, or if the authors say they used 'blocks of 4' but the final numbers differ by 6)?

Studies assessed as being potentially 'high risk' will be not be included in the review. Where a study is classified as 'high risk' for one or more of the above criteria we will attempt to contact the study authors to address any possible lack of information/concerns. If adequate information remains unavailable, the study will remain in 'awaiting classification' and the reasons and communications with the author (or lack of) described in detail.

The process is described in full in Figure 1.

CONTRIBUTIONS OF AUTHORS

Katie Webster: scoped, designed and drafted the protocol with the help of the other authors.

Natasha A Harrington-Benton: patient/public guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Owen Judd: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Diego Kaski: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Otto R Maarsingh: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

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Samuel MacKeith: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Jaydip Ray: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Vincent A Van Vugt: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Martin J Burton: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

DECLARATIONS OF INTEREST

Katie Webster: none known.

Natasha A Harrington-Benton: Natasha Harrington-Benton is the Director of the Ménière's Society, a national charity supporting people with vestibular conditions. The Ménière's Society supports research in various ways, including distributing surveys and/or providing grant funding for projects studying vestibular conditions. Some of the studies they have previously funded may be included in the review. They do not carry out the research themselves and are not directly involved in projects.

Owen Judd: none known.

Diego Kaski: none known.

Otto R Maarsingh: none known.

Samuel MacKeith: Samuel MacKeith is the Assistant Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this protocol.

Jaydip Ray: none known.

Vincent A Van Vugt: none known.

Martin J Burton: Martin Burton undertook private practice until March 2020 and saw some patients with Ménière's disease. He is the Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this protocol.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

  Infrastructure funding for Cochrane ENT
- National Institute for Health Research, UK

  This project is funded by the National Institute for Health Research (NIHR) Evidence Synthesis Programme (NIHR132217). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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