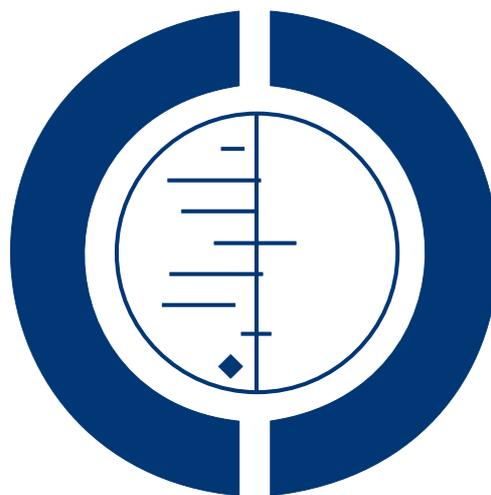


# Intratympanic steroids for Ménière's disease or syndrome (Review)

Phillips JS, Westerberg B



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## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	4
METHODS . . . . .	4
RESULTS . . . . .	7
Figure 1. . . . .	9
DISCUSSION . . . . .	11
AUTHORS' CONCLUSIONS . . . . .	11
ACKNOWLEDGEMENTS . . . . .	11
REFERENCES . . . . .	12
CHARACTERISTICS OF STUDIES . . . . .	14
DATA AND ANALYSES . . . . .	19
APPENDICES . . . . .	19
HISTORY . . . . .	21
CONTRIBUTIONS OF AUTHORS . . . . .	21
DECLARATIONS OF INTEREST . . . . .	21
SOURCES OF SUPPORT . . . . .	21
INDEX TERMS . . . . .	21

[Intervention Review]

# Intratympanic steroids for Ménière's disease or syndrome

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## ABSTRACT

### Background

Ménière's disease is a disorder characterised by hearing loss, tinnitus and disabling vertigo. The use of intratympanic steroids to reduce the severity of these symptoms has been gaining popularity.

### Objectives

To assess the effectiveness of intratympanic steroids on the frequency and severity of attacks of vertigo, on chronic symptoms such as tinnitus, imbalance and hearing loss, and on the progression of these symptoms in patients with definite Ménière's disease or syndrome, as defined by the AAO-HNS Committee.

### Search strategy

We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the most recent search was 13 January 2011.

### Selection criteria

Randomised controlled trials of intratympanic dexamethasone versus placebo in patients with Ménière's disease.

### Data collection and analysis

Two authors independently assessed trial risk of bias and extracted data. We contacted study authors for further information where possible.

### Main results

A single trial containing 22 patients, with a low risk of bias was included. This trial found that after 24 months, compared with placebo, the use of intratympanic dexamethasone demonstrated a statistically significant improvement in vertigo as defined by a respective improvement in functional level (90% versus 42%), class (82% versus 57%), change in Dizziness Handicap Inventory scores (60.4 versus 41.3) and mean vertigo subjective improvement (90% versus 57%). The treatment regime described by the authors involved daily injections of dexamethasone solution 4 mg/ml for five consecutive days. These results were clinically significant. No complications were reported.

## Authors' conclusions

The results of a single trial provide limited evidence to support the effectiveness of intratympanic steroids in patients with Ménière's disease. This trial demonstrated a statistically and clinically significant improvement of the frequency and severity of vertigo measured 24 months after the treatment was administered. It is important to note that there were a few aspects of the study which we were unable to clarify with the study authors.

## PLAIN LANGUAGE SUMMARY

### Intratympanic steroids for Ménière's disease or syndrome

Ménière's disease is a disorder of the inner ear which results in a spinning form of dizziness (vertigo), hearing loss and ringing in the ear (tinnitus); this can be very disabling. The cause of Ménière's disease is unknown. There has been some support in the medical literature for a course of treatment that involves the injection of steroids through the eardrum and into the middle ear to reduce the frequency and severity of these symptoms.

We looked for studies which compared steroid injections in the ear with placebo in patients with Ménière's disease or syndrome. Only one study satisfied the prespecified inclusion criteria for this review. This study demonstrated a benefit of this treatment for patients with Ménière's disease; at 24 months the patients in the treatment group had far fewer episodes of vertigo. The results of this review are encouraging, however as it is based solely on the results of a single study, further research is required.

## BACKGROUND

### Description of the condition

#### Definition

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

#### Aetiology

Ménière's disease is thought to be associated with endolymphatic hydrops, i.e. raised endolymph pressure in the membranous labyrinth of the inner ear (Hallpike 1938). The cause of the hydrops is not known in most cases. Specific disorders affecting the inner ear which are also associated with hydrops include temporal bone fracture, syphilis, hypothyroidism, Cogan's syndrome and Mondini dysplasia.

#### Prevalence

Ménière's disease is most common between 40 and 60 years of age, although younger people can also be affected (da Costa 2002; Morales 2003; Takeda 1998; Watanabe 1995). 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). Acute episodes of Ménière's tend to occur in clusters with a mean frequency of between six and 11 clusters per year, although remission may last several months. Episodes have been observed to occur with increasing frequency over the first few years after presentation and then decrease in association with a sustained deterioration in hearing (Moffat 1997). In most cases vertiginous episodes eventually cease completely (Silverstein 1989). This fluctuating character of the disease is an aspect of the natural history that makes formal evaluation of any treatment effect in patients with Ménière's disease difficult.

#### Diagnosis

The disorder is not always easy to diagnose and there is no 'gold standard' diagnostic test. It is almost certainly over-diagnosed by non-specialists. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic

guidelines (Alford 1972) which have been revised twice (Ménière's Guide 1995; Pearson 1985), but these are not universally accepted. Nevertheless, they provide a standard which can be applied easily to make the diagnosis in normal clinical practice. In brief, these guidelines now stipulate that a 'definite' diagnosis can only be made on the basis of:

1. at least two spontaneous episodes of rotational vertigo lasting at least 20 minutes;
2. audiometric confirmation of a sensorineural hearing loss;
3. tinnitus and/or a perception of aural fullness.

These criteria exclude most other vestibular conditions, but further investigation is also necessary to exclude other disease processes, such as an acoustic neuroma.

## Treatment

Ideally, the aim of treatment is to:

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

No treatment modality has been shown to achieve all of these aims. In fact an evidence base for the management of patients with Ménière's disease is sadly lacking. Many treatment modalities exist. Broadly speaking these include dietary and lifestyle adjustments, complementary and alternative medicine, a variety of devices, rehabilitative therapies, medicines and surgery. The two main conservative medical treatment modalities are betahistine therapy and diuretics. Both of these treatments have been assessed formally by Cochrane Review (Burgess 2009; James 2001). Betahistine is thought to exert its effect by either reducing the endolymphatic pressure through improved circulation in the stria vascularis or inhibiting activity in the vestibular nuclei. The Cochrane Review concluded that there was insufficient evidence to support betahistine as an effective treatment for patients with Ménière's disease. Diuretics are believed to work by reducing the volume (and therefore also the pressure) of these fluids. The Cochrane Review concluded that there was insufficient evidence about the effect of diuretics on the symptoms of Ménière's disease and that further research was required. Intratympanic gentamicin is a treatment for Ménière's disease that works by abolishing the function of the labyrinth and is the subject of another Cochrane Review (Pullens 2011). Surgical treatments have also been proposed for the management of Ménière's disease and there are two types. Destructive surgery aims to control individual symptoms by abolishing vestibular function; non-destructive surgery aims to alter the natural course of the disease. A Cochrane Review, however, has recently been completed and identified only two randomised controlled trials of endolymphatic sac surgery; one comparing it to placebo

surgery and the other to a different type of surgery. Neither trial detected a significant difference between the treatment and control group (Pullens 2010).

## Description of the intervention

The use of intratympanic glucocorticoids involves the injection or instillation of glucocorticoid solution through the tympanic membrane into the middle ear. From here it is proposed that the drug is absorbed into the inner ear perilymph primarily via the round window membrane, but also via the oval window annular ligament and the small lacunar mesh in the bone wall surrounding the inner ear.

Pharmacokinetic studies in animals and humans have shown that only high doses of systemic glucocorticoids will result in detectable drug levels in the inner ear perilymph and that substances applied to the round window membrane lead to significantly higher drug levels in the inner ear fluids compared to systemic application (Bachmann 2001; Bird 2007; Chandrasekhar 2000; Niedermeier 2003; Parnes 1999).

Local intratympanic application of drugs for the treatment of inner ear diseases has advantages over systemic treatment. These are i) the bypassing of the blood-labyrinthine barrier, resulting in ii) higher concentrations in the inner ear fluids despite the lower total amount of drug given and iii) avoiding the major unwanted effects of systemically administered medications. During the last decade, a rapidly growing number of reports have been published on treatment results of intratympanic application of glucocorticoids for inner ear disorders, including Ménière's disease (Lustig 2004). The use of intratympanic glucocorticoids for the treatment of sudden sensorineural hearing loss is the subject of another Cochrane Review (Plontke 2009).

Variations exist between the particular type of glucocorticoid used, the dosage administered and the total duration of treatment. The use of intratympanic steroids is a well-tolerated, safe office procedure. Sakata was first to investigate the therapeutic use of intratympanic steroids for Ménière's disease in 1987, and along with Itoh reported the outcome in 61 patients (Itoh 1991). None of the patients reported any adverse effects from the treatment.

## How the intervention might work

Interest in the role of steroids for the treatment of inner ear diseases originates from work done by McCabe in the late 1970s (McCabe 1979). Since then work supporting the theory that Ménière's disease is an immune-mediated disorder of the endolymphatic sac has strengthened the proposed role of steroids for the treatment of Ménière's disease. The elevation of immune complexes (Brookes 1986; Derebery 1991; Gutierrez 1994), autoimmune responses to type II collagen (Yoo 1984; Yoo 1985), autoimmune responses to other inner ear antigens (Suzuki 1997; Yoo 2001), focal inflam-

mation within the endolymphatic sac (Danckwardt-Lillieström 2000), IgG deposits in the endolymphatic sac (Dornhoffer 1993), autoantibodies to the endolymphatic sac (Alleman 1997) and many other specific and non-specific determinants of immune-mediated disease (Savastano 2007) have all been demonstrated in patients with Ménière's disease. Furthermore, experimental studies have identified glucocorticoid receptors within a variety of crucial inner ear structures, particularly the cochlea, vestibular tissues and spiral ligament (Rarey 1996).

Intratympanic steroids are used in patients with Ménière's disease with the aim of:

1. reducing the number and severity of acute attacks of vertigo;
2. aborting or ameliorating the hearing loss and tinnitus associated with such attacks;
3. alleviating any chronic symptoms (e.g. tinnitus and imbalance);
4. preventing progression of the disease, in particular the loss of hearing and balance function which characterises the disorder.

## Why it is important to do this review

The use of intratympanic glucocorticoids for the treatment of Ménière's disease is becoming ever more popular given a relative lack of other effective treatments; this is despite no formal systematic appraisal of the literature. Specifically there is uncertainty as to whether intratympanic glucocorticoids are better than placebo or no treatment. A Cochrane Review is therefore warranted to assess the benefits and harms of intratympanic glucocorticoids for the treatment of Ménière's disease.

## OBJECTIVES

We aimed to assess the effect of intratympanic glucocorticoids on the frequency and severity of attacks of vertigo, on chronic symptoms such as tinnitus, imbalance and hearing loss and on the progression of these symptoms in patients with definite Ménière's disease or syndrome, as defined by the AAO-HNS Committee.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials of intratympanic glucocorticoids versus placebo. We preferred trials analysed on an intention-to-treat basis and where necessary and possible we planned to reconstruct intention-to-treat analyses.

#### Types of participants

Patients of any age with Ménière's disease or syndrome. We graded studies on the basis of the robustness of the methods used to diagnose these disorders and this grading was to form the basis of a sensitivity analysis:

- Grade I - studies in which the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) 1995 criteria have been used and only patients with definite Ménière's included in the study.
- Grade II - studies in which clear but less rigorous criteria have been used.
- Grade III - studies in which the measures used are considered inadequate.

Studies that distinguished patients with Ménière's syndrome but did not use an appropriate criteria were to be considered separately. As in the Cochrane Review of betahistine (James 2001), we aimed to focus on studies employing strict criteria for the diagnosis of Ménière's to try to address the specific question of the effects of drugs in patients with 'definite' Ménière's disease or syndrome. Priority was to be given to trials studying patients who had not received steroids for any reason in the past.

#### Types of interventions

Intratympanic glucocorticoids, for example dexamethasone, (methyl-)prednisolone and hydrocortisone, versus placebo. Other medication could be used concurrently provided it was used equally in each group. We decided to compare intratympanic glucocorticoids with placebo as no 'gold standard' treatment for Ménière's is available. We excluded any trials with no placebo group as there is a significant placebo effect and spontaneous resolution in Ménière's management. We only included trials with a cross-over design if data from results before the cross-over were extractable, in order to avoid the potential confounding effect of a carry-over phenomenon.

The intervention had to be delivered using one of the following drug delivery systems (i.e. routes of intratympanic drug administration):

- single or repeated intratympanic injection with or without volume stabilisation and with or without visualisation of the round window membrane; or
- continuous or discontinuous drug application via partly or fully implantable pump systems; or
- application by surgical tympanostomy and the placement of steroid soaked pledgets.

We considered other methods of drug delivery as long as the applied substance ultimately entered the inner ear.

#### Types of outcome measures

Important outcomes were as follows.

1. Number and severity of acute attacks of vertigo.
2. Changes in hearing.
3. Severity of tinnitus.
4. Changes in perception of aural fullness.
5. Functional impairment and disability.
6. Overall changes in well-being and quality of life.
7. Side effects of the treatment.

If disease was bilateral and asymmetrical, we planned to assess outcomes 2, 3 and 4 using the injected ear.

We planned to measure outcomes in the short-term (< 18 months) or long-term (> 18 months). The prevention of progressive hearing loss is equally important but must be measured over a period of many months or years.

Ménière's is a chronic disease with a fluctuating and episodic pattern of symptoms, therefore assessment of long-term effectiveness of any therapy is extremely important. Ideally trials should have evaluated both the longer-term effects of both short courses of treatment (two to 12 weeks), and the effectiveness of longer-term (more than three months) treatment. Long-term outcomes should be assessed at 18 to 24 months and 42 to 48 months after the onset of treatment, as suggested by the AAO-HNS ([Ménière's Guide 1995](#)).

The severity of the disease and the time elapsed before treatment could be an important factor in determining response to intratympanic glucocorticoids and we followed the same staging system as [James 2001](#) to address this issue in more detail.

The AAO-HNS 1995 guidelines for the evaluation of treatment of Ménière's disease are designed to evaluate the long-term effects of specific (usually surgical) intervention ([Ménière's Guide 1995](#)).

However, like the diagnostic criteria referred to above, they are well-defined and rigorous.

In outline:

1. the number of vertiginous episodes per unit time is recorded with and without treatment;
2. hearing is assessed by four-tone average of pure-tone threshold at 0.5, 1, 2 and 3 kHz on audiogram;
3. functional impairment is assessed with a scale measuring daily tasks;
4. objective measures for assessment of tinnitus and perception of aural fullness have not been defined.

We planned to categorise studies on the similarity of their outcome measures to AAO-HNS guidelines ([Ménière's Guide 1995](#)). Studies using similar measures will be graded (I), dissimilar but appropriate measures (II), and those using measures considered inadequate will be graded (III). This was to be used to form the basis for a sensitivity analysis.

The AAO-HNS guidelines use a number of scales to define the frequency and severity of vertiginous episodes. These scales are outlined in [Table 1](#) and [Table 2](#) ([Ménière's Guide 1995](#)). Another commonly used tool to assess the effects of dizziness is the Dizziness Handicap Inventory (DHI) ([Jacobson 1990](#)). This tool is administered as a questionnaire and is composed of 25 questions that have been developed to evaluate the self-perceived handicapping effects imposed by vestibular disease. Similarly the effects of tinnitus may be assessed using the Tinnitus Handicap Inventory (THI) whereby a questionnaire is completed to evaluate the self-perceived impact of tinnitus.

**Table 1. Functional level scale**

Regarding my current state of overall function, not just during attacks (check the ONE that best applies):

1. My dizziness has no effect on my activities at all. 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.
2. 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.
3. I am able to work, drive, travel, take care of a family or engage in most 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.
4. 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.
5. Even essential activities must be limited. I am disabled.
6. I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.

**Table 2. Class as an outcome measure of vertigo**

Numerical value	Class
0	A (complete control of definitive spells)
1 to 40	B
41 to 80	C
81 to 120	D
> 129	E
Secondary treatment initiated due to disability from vertigo	F

Numerical value =  $(X/Y) \times 100$ , rounded to the nearest whole number, where X is the average number of definitive spells per month for the 6 months 18 to 24 months after therapy and Y is the average number of definitive spells per month for the 6 months before therapy

### Search methods for identification of studies

We conducted systematic searches for randomised controlled trials. There were no language, publication year or publication status restrictions. The date of the last search was 13 January 2011.

#### Electronic searches

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

We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2, Box 6.4.b. ([Handbook 2011](#))). Search strategies for the major databases including CENTRAL are provided in [Appendix 1](#).

#### Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition,

we searched PubMed, TRIPdatabase, NHS Evidence - ENT & Audiology, and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.

#### Data collection and analysis

Only one study was included in this review, therefore some of the methods of analysis described below were not applicable for the current version of this review but may be applied in future updates once further studies are identified.

#### Selection of studies

The two authors independently assessed the references retrieved to identify studies which met the inclusion criteria outlined above. Where there was disagreement we resolved this by discussion.

#### Data extraction and management

We extracted data onto standardised, pre-piloted forms. We contacted study authors where necessary for clarification.

#### Assessment of risk of bias in included studies

JP and BW undertook assessment of the risk of bias of the included trials independently with the following taken into consideration,

as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

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

We used the Cochrane 'Risk of bias' tool in RevMan 5.1 (RevMan 2011), which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry. This involved making a judgement of low risk of bias, high risk of bias or unclear (or unknown) risk of bias.

### Measures of treatment effect

We anticipated that study outcomes would be measured in a variety of ways using continuous, discrete and categorical variables. We planned to dichotomise data where appropriate. We also planned to seek statistical advice, as necessary, to determine the best way of presenting and summarising the data.

### Data synthesis

Data analysis was to be by intention-to-treat. If data were compatible and of sufficient quality (outcome measure categories (I) or (II)), they were to be combined to give a summary measure of effect, otherwise we would not combine data.

### Subgroup analysis and investigation of heterogeneity

We planned, if possible, to compare the effect of different doses of glucocorticoids. If sufficient data were available we planned to carry out subgroup analyses, grouping patients by duration and severity of disease.

### Sensitivity analysis

We planned to use study quality in a sensitivity analysis.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

### Results of the search

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The searches carried out in April 2010 and January 2011 identified a total of 235 articles and we reviewed these against our inclusion criteria. We considered six articles to be potentially relevant and retrieved these in full text but subsequently excluded two (see [Excluded studies](#)). We identified two further articles as 'in progress'; one was relevant ([Otonomy 2010](#)) and the other ([Imperial College 2010](#)) will compare intratympanic steroids with intratympanic gentamicin (so on completion will be excluded from this review as it is not placebo-controlled) (see [Characteristics of ongoing studies](#)). We then further considered four articles, describing a single study, for inclusion in our review ([Garduno-Anaya 2003](#), [Garduno-Anaya 2005a](#), [Garduno-Anaya 2005b](#), [Garduno-Anaya 2005c](#) - see [Garduno-Anaya 2005](#) for all references).

### Included studies

We considered that the four articles mentioned above described the same study but at different stages of data analysis. Two of the articles presented results after two years and two presented results after four years (see [Garduno-Anaya 2005](#)). All four articles had the same lead author and the main co-authors remained for most of the articles. The number of participants described throughout all four articles was identical and there were no discrepancies found upon cross-referencing data between each article. Three of the articles were abstracts and of these the contents of two were almost identical (2005 abstracts). All attempts to contact any of the authors of these articles, firstly to clarify that they all indeed represent the same study and secondly to obtain further data for analysis, were unsuccessful.

Most of the information in this review has been derived from the only full-text article we had available ([Garduno-Anaya 2005](#), published in *Otolaryngology - Head and Neck Surgery*). The study was a two-year prospective, placebo-controlled, double-blind, randomised trial that took place in the Department of Neurology of the National Institute of Neurology and Neurosurgery in Mexico City.

### Participants

All participants were defined as having 'definite' Ménière's disease as outlined by the 1995 American Academy of Otolaryngology - Head and Neck Surgery Committee on Hearing and Equilibrium (Grade I), and being classified at Shea's stage III, in which hearing loss is for all tones, with poor speech discrimination, but fullness, dizzy spells and tinnitus are the chief complaints. Participants were adults over the age of 18 who had not undergone any previous treatment with either steroids or surgery. Before inclusion into the study participants had failed to benefit from a six-month course of conventional medical therapy. Conventional medical therapy

was defined as caffeine and salt restriction (< 1500 mg/day), a vasodilator and a diuretic.

### Interventions

Patients were randomised into two groups; one group was injected intratympanically with dexamethasone 4 mg/ml and the other group was injected with a placebo. The exact placebo drug was not mentioned. All subjects received daily injections every day for a total of five days.

### Outcome measures

Outcome measures were recorded at 1, 6, 12, 18 and 24 months following the procedure. Four outcome measures were recorded for vertigo (functional level - as defined by the AAO-HNS; class - as defined by the AAO-HNS ([Mènière's Guide 1995](#)); Dizziness Handicap Inventory score; and vertigo subjective improvement). Three outcome measures were recorded for hearing loss (pure-tone average, speech discrimination score and hearing loss subjective improvement). Three outcome measures were recorded for tinnitus (Tinnitus Handicap Inventory score, grading of tinnitus severity and tinnitus subjective improvement). One measure was recorded to reflect aural fullness (subjective aural improvement). Electrophysiological tests were also performed: electronystagmog-

raphy (including vestibular response to caloric stimuli) and extratympanic electrocochleography. Two of the abstracts reported results at 48 months. Vertigo subjective improvement was defined using a scale from 0 to 10, in which the subject was asked to rate any improvement in vertigo where 0 was no change and 10 represented 100% improvement. A similar scale was used to assess subjective improvement in hearing loss, tinnitus and aural fullness.

### Excluded studies

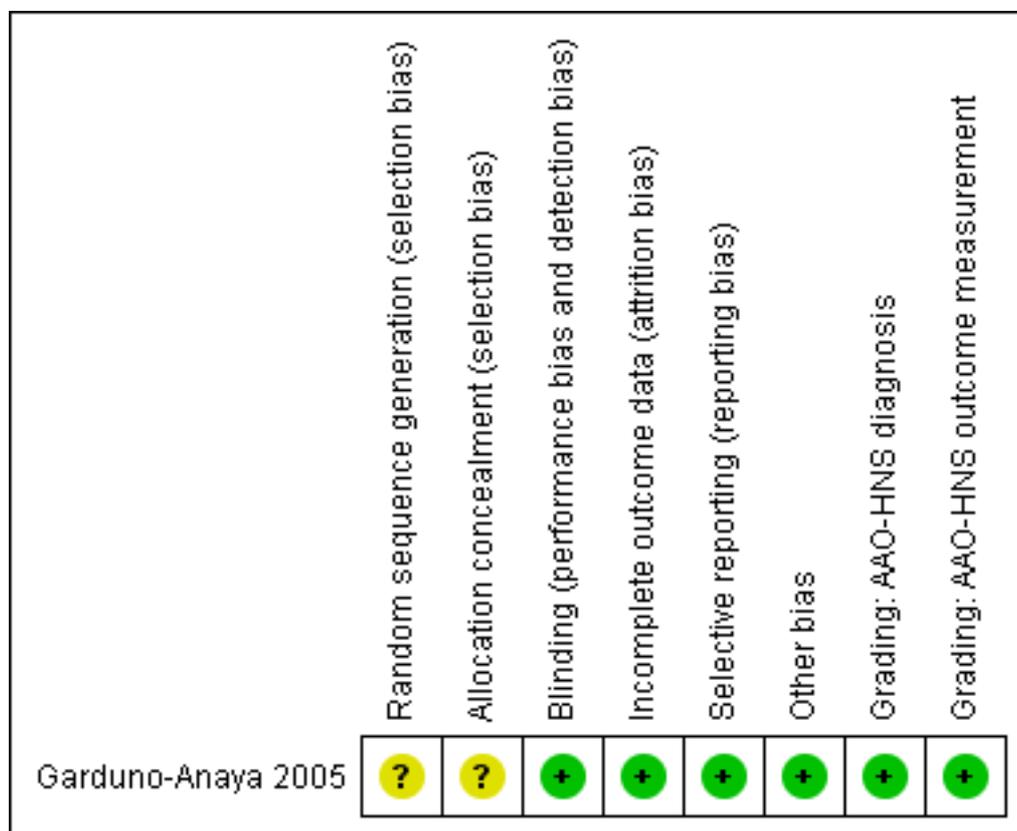
We excluded [Silverstein 1998](#) as it was a cross-over study. We attempted to obtain data comparing the two arms prior to cross-over, however we were not able to obtain these data from the author. We excluded [Paragache 2005](#) as concurrent medication was used in only one of the intervention groups.

### Risk of bias in included studies

For this study the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) 1995 criteria were used and only patients with definite Mènière's included in the study (Grade I). Long-term outcomes were assessed at 24 months after the onset of treatment, as suggested by the AAO-HNS.

There was some risk of bias in the included study as depicted in the [Characteristics of included studies](#) table and [Figure 1](#).

**Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**



The authors describe a double-blind randomised trial but we were unable to verify the exact methods employed to achieve blinding or randomisation. For this reason we have judged adequacy of sequence generation and allocation concealment to be 'unclear'.

### Effects of interventions

No meta-analysis was possible as only one study was included in this review ([Garduno-Anaya 2005](#)).

### Number and severity of acute attacks of vertigo

Comparing the treatment group (dexamethasone) with the placebo group at 24 months demonstrated a statistically significant improvement in vertigo as defined by a respective improvement in functional level (90% versus 42% of patients achieving level 1,  $P < 0.001$ ), class (82% versus 57% of patients achieving class A - complete control,  $P < 0.001$ ), change in Dizziness Handicap Inventory (DHI) scores (60.4 versus 41.3) and mean vertigo subjective improvement (90% versus 57%). All of the patients in the treatment group completed the study, however five patients (45%) from the control group were rated as failure (class F) and

had to be given another treatment for their continuing vertigo.

### Changes in hearing

At 24 months, there was a statistically significant improvement in mean hearing loss subjective improvement (35% versus 10%), however there was no statistically significant improvement in any of the other two measures of hearing loss, such as pure-tone average or speech discrimination score.

### Severity of tinnitus and changes in perception of aural fullness

At 24 months, it was reported that there was a statistically significant improvement in tinnitus subjective improvement and aural subjective improvement: a mean improvement of 48.1% versus 20%. However, the original text was ambiguous in its description of these results and did not explain whether these were the results for one or both measures. We were unable to verify any of the

data with the study authors. There was no statistically significant improvement in any of the other two measures of tinnitus, such as the Tinnitus Handicap Inventory score or the grading of tinnitus severity.

### Side effects of the treatment

It was stated that there were no reported side effects or complications in either group.

A summary of the results for each outcome measure assessed in Garduno-Anaya 2005 can be found in Table 3.

**Table 3. Garduno-Anaya 2005 - summary of results**

Dexamethasone group (D) versus placebo group (P) at 24 months follow up						
Functional level	Class	Dizziness Handicap Inventory	Vertigo subjective improvement	Pure-tone average	Speech discrimination score	Hearing loss subjective improvement
Level 1 was achieved by 90% (D) versus 42% (P) <i>Statistically significant difference (P &lt; 0.001)</i>	Class A (complete control) in 82% (D) versus 57% (P) <i>Statistically significant difference (P &lt; 0.001)</i> All of the patients in the treatment group completed the study, however 5 patients (45%) from the control group were rated as failure (class F) and had to be given another treatment for their continuing vertigo	Change in score 60.4 (D) versus 41.3 (P) <i>Statistically significant difference (P &lt; 0.008)</i>	Mean improvement 90% (D) versus 57% (P) <i>Statistically significant difference (P &lt; 0.001)</i>	<i>No statistically significant difference</i>	<i>No statistically significant difference</i>	Mean improvement 35% (D) versus 10% (P) <i>Statistical significant difference (P &lt; 0.001)</i>
Tinnitus Handicap Inventory score	Grading of tinnitus severity	Tinnitus subjective improvement	Aural subjective improvement	Electronystagmography	Extra-tympanic electrocochleography	
<i>No statistically significant difference</i>	<i>No statistically significant difference</i>	<i>Original text ambiguous</i>	<i>Original text ambiguous</i>	<i>No statistically significant difference</i>	<i>No statistically significant difference</i>	

## DISCUSSION

### Summary of main results

A single double-blind, randomised trial ([Garduno-Anaya 2005](#)) treated patients with definite Ménière's disease (Shea's stage III) who were unresponsive to medical therapy with dexamethasone (4 mg/ml) inner ear perfusion for one hour daily for five days. This study demonstrated a statistically significant improvement in the frequency and severity of vertigo in the treatment group as compared to the placebo group at 24 months.

### Overall completeness and applicability of evidence

Whilst searching for appropriate articles for this review, one study was identified as being ongoing ([Otonomy 2010](#)). When the results of this trial are reported, the findings of this review may be updated to provide better quality evidence.

### Quality of the evidence

Overall the Garduno-Anaya study was well-designed and free of overt bias. The main challenge facing the authors of this review were related to contacting the authors of the Garduno-Anaya study to clarify certain aspects of the trial. Additionally the review authors were unable to clarify a small number of ambiguities within the study results section.

### Agreements and disagreements with other studies or reviews

A number of other non-Cochrane reviews and editorials have been written about the use of intratympanic steroids for inner ear conditions as a whole ([Alles 2006](#); [Doyle 2004](#); [Harris 2007](#); [Hamid 2008](#); [Hu 2009](#)). Unfortunately half of these reviews were written before the publication of the Garduno-Anaya study ([Alles 2006](#); [Doyle 2004](#)). The editorial by Harris ([Harris 2007](#)) and the review articles by Hamid and Hu ([Hamid 2008](#); [Hu 2009](#)) acknowledge the results of the Garduno-Anaya study but recommend the production of further randomised, placebo-controlled trials so that more robust conclusions may be made, based on more than just a single study. Both Hamid and Hu ([Hamid 2008](#); [Hu 2009](#)) cite the outcome of two prospective randomised controlled trials; one of these trials was included in this review ([Garduno-Anaya 2005](#)) and the other trial was acknowledged by this review but excluded as it was a cross-over trial ([Silverstein 1998](#)). The reviews by Hamid and Hu ([Hamid 2008](#); [Hu 2009](#)) raise the issue that these two studies produced conflicting results. We feel that no conflict exists

as the Silverstein study did not meet our criteria for inclusion. We decided not to include cross-over studies as the final results of such a study could be a carry-over effect from the first treatment; this was also concluded by Hu ([Hu 2009](#)).

## AUTHORS' CONCLUSIONS

### Implications for practice

There is limited evidence to support the effectiveness of intratympanic steroids in patients with Ménière's disease based on a single double-blind, randomised study, with no complications described. The treatment effect was reported mainly with respect the improvement of the frequency and severity of vertigo. This effect was measured 24 months after the treatment was administered. It must be emphasised that this study included a relatively small number of participants and that there were a few aspects of the study which we were unable to clarify with the study authors.

### Implications for research

This review is based on the outcome of a single, double-blinded, randomised study. There is a need for more randomised controlled trials in the future, involving larger numbers of participants, so that the results of this review can be either substantiated or contested. With respect to the subject of this particular review, we would recommend placebo-controlled trials rather than trials that compare different treatment strategies due to the nature of disease progression in Ménière's disease. Cross-over trials are not recommended. Treatment arms should be designed so that if other therapies are used concurrently, they are administered in an equal manner for both groups. Due to the prevalence of Ménière's disease multi-centre trials may be required to provide the necessary numbers of participants to achieve significant outcome data. Future studies should comply with the reporting standards as set out in the CONSORT 2010 statement ([CONSORT 2010](#)). Prior registration of planned trials in trial registries is also recommended for transparency.

## ACKNOWLEDGEMENTS

We wish to thank Jenny Bellorini for her editorial help and Gemma Sandberg for her help with the search strategies. We would like to acknowledge the work done by the authors of reviews that consider other treatment options for Ménière's disease ([Burgess 2009](#); [James 2001](#); [Pullens 2010](#); [Pullens 2011](#)) and the use of intratympanic glucocorticoids for other conditions ([Plontke 2009](#)). This review shares a similar format to conserve clarity with respect to these reviews as they cover similar topics.



**Danckwardt-Lillieström 2000**

Danckwardt-Lillieström N, Friberg U, Kinnefors A, Rask-Andersen H. Ultrastructural analysis of 20 intraosseous endolymphatic sacs from patients with cerebello-pontine angle tumours. A surgically obtained control material for histopathological studies. *Auris Nasus Larynx* 2000;**27**(4): 311–21.

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**Hu 2009**

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James AL, Burton ML. Betahistine for Ménière's disease or syndrome. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD001873]

**Lustig 2004**

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McCabe BF. Autoimmune sensorineural hearing loss. *Annals of Otology, Rhinology and Laryngology* 1979;**88**(5 Pt 1):585–9.

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**Morales 2003**

Morales Angulo C, Gomez Castellanos R, Garcia Mantilla J, Bezos Capelastegui JT, Carrera F. Epidemiology of Meniere's disease in Cantabria. *Acta Otorrinolaringológica Española* 2003;**54**(9):601–5.

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**Pullens 2011**

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**Yoo 2001**

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Garduno-Anaya 2005

Methods	Prospective, randomised, double-blind, placebo-controlled study
Participants	n = 22 'Definite' Ménière's disease as outlined by the 1995 American Academy of Otolaryngology - Head and Neck Surgery Committee on Hearing and Equilibrium Shea's stage III at baseline Failed medical management
Interventions	Group 1: dexamethasone 4 mg/ml Group 2: placebo (exact compound not defined by authors)
Outcomes	Vertigo: Functional level Class Dizziness Handicap Inventory (DHI) score Vertigo subjective improvement (VSI) Hearing loss: Pure-tone average (PTA) Speech discrimination score (SD) Hearing loss subjective improvement (HLSI) Tinnitus: Tinnitus Handicap Inventory score (THI) Grading of tinnitus severity (GTS) Tinnitus subjective improvement (TSI) Aural fullness: Aural subjective improvement (ASI) Electrophysiological tests: Electronystagmography including vestibular response to caloric stimuli (ENG) Extra-tympanic electrocochleography (ECoG)
Notes	-

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was a randomised trial, however the method employed was not detailed in the articles available and we were unable to contact the study authors for clarification
Allocation concealment (selection bias)	Unclear risk	This was not detailed in the articles available and we were unable to contact the study authors for clarification

**Garduno-Anaya 2005** (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	This study was defined as double-blinded, however details regarding the methods used to achieve blinding were not detailed in the articles available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data were addressed appropriately
Selective reporting (reporting bias)	Low risk	All data were presented in full in an appropriate manner
Other bias	Low risk	The study authors provide baseline values for 4 variables; 2 of these are measures of hearing and 2 are measures of vertigo. The difference in initial hearing measures between the dexamethasone group and the control group is less important as no statistically significant differences in outcome between the dexamethasone and control groups were reported for outcome measures relating to hearing. The baseline measures for vertigo do start off slightly lower in the dexamethasone group. However, this is balanced by the significant size in treatment effect in the dexamethasone group as compared with the control group. This difference was significant both statistically and clinically. In view of this we concluded that this initial difference is worthy of note, but was not sufficient to introduce significant bias. No other sources of potential bias were identified
Grading: AAO-HNS diagnosis	Low risk	All participants were defined as having 'definite' Ménière's disease as outlined by the 1995 American Academy of Otolaryngology - Head and Neck Surgery Committee on Hearing and Equilibrium (Grade I)
Grading: AAO-HNS outcome measurement	Low risk	Outcome measures were recorded at 24 months following the procedure

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

Study	Reason for exclusion
Paragache 2005	<p>ALLOCATION: Prospective, randomised, placebo-controlled study</p> <p>PARTICIPANTS: n = 40 Definite Ménière's disease as outlined by the 1995 American Academy of Otolaryngology - Head and Neck Surgery Committee on Hearing and Equilibrium</p> <p>INTERVENTIONS: Group 1: dexamethasone 2 mg/ml Group 2: salt and caffeine restricted diet, nicotine and alcohol restrictions. Betahistine hydrochloride 16 mg tds for maintenance therapy (Our protocol stated that "Other medication may be used concurrently provided it is used equally in each group")</p>
Silverstein 1998	<p>ALLOCATION: Prospective, randomised, double-blind, cross-over trial in 20 patients with either definite or probable Ménière's disease as defined by the American Academy of Otolaryngology - Head and Neck Surgery Committee on Hearing and Equilibrium. Group 1: intratympanic dexamethasone 8 mg/ml daily over 3 consecutive days; Group 2: intratympanic normal saline daily over 3 consecutive days Cross-over trials are excluded from this review; JP contacted the authors to obtain 'pre-cross-over data', but no data were available</p>

tds: three times a day

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

### Imperial College 2010

Trial name or title	Transtympanic gentamicin vs. steroids in refractory Ménière's disease
Methods	Randomised, double-blind
Participants	Patients aged 18 to 70 years with unilateral Ménière's disease (definite or probable, according to Committee on Hearing and Equilibrium guidelines, 1995) with hearing loss and presenting with recurrent vertigo, not responding to medical treatment for at least 6 months with normal, age-appropriate hearing in the contralateral ear
Interventions	Methylprednisolone (2 transtympanic injections at an interval of 2 weeks) versus gentamicin (2 transtympanic injections at an interval of 2 weeks)
Outcomes	Primary outcome measures: control of vertigo attacks as determined by validated questionnaires and as per committee on hearing and equilibrium guidelines Secondary outcome measures: changes in hearing outcome as determined by hearing tests
Starting date	April 2009

**Imperial College 2010** (Continued)

Contact information	Dr Adolfo M Bronstein, Imperial College London, UK
Notes	Study does not evaluate intratympanic steroids versus placebo and will not therefore fulfil the inclusion criteria for this review

**Otonomy 2010**

Trial name or title	OTO-104 for Ménière's disease
Methods	Prospective, randomised, double-blind, placebo-controlled, multi-centre, phase 1B study
Participants	Both sexes aged 18 years to 75 years
Interventions	Group 1: OTO-104 (steroid) 3 mg Group 2: placebo Group 3: OTO-104 (steroid) 12 mg
Outcomes	Primary outcome measures: 1. Safety and tolerability Secondary outcome measures: 1. Clinical activity of 2 OTO-104 doses relative to placebo (change in baseline for vertigo frequency will be evaluated with descriptive statistics) 2. The impact of tinnitus on activities of daily living 3. Hearing loss in the affected ear by audiometric evaluation 4. Quality of life using a patient-reported questionnaire 5. Severity of vertigo episodes using a patient-reported vertigo score
Starting date	March 2010
Contact information	Carl LeBel, PhD, Chief Scientific Officer, Otonomy, Inc, USA
Notes	-

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix I. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)	CINAHL (EBSCO)
<p>#1 transtympanic* OR intratympanic* OR tympanic OR topical* OR local* OR ITS OR (MIDDLE NEAR EAR) OR (INNER NEAR EAR)</p> <p>#2 MeSH descriptor Ear explode all trees</p> <p>#3 MeSH descriptor Drug Administration Routes explode all trees</p> <p>#4 (#1 OR #2 OR #3)</p> <p>#5 MeSH descriptor Steroids explode all trees</p> <p>#6 MeSH descriptor Glucocorticoids explode all trees</p> <p>#7 Beclomethasone OR Betamethasone OR Budesonide OR Clobetasol OR Desoximetasone OR Dexamethasone OR Dexamethasone Isonicotinate OR Diflucortolone OR Flumethasone OR Fluocinolone Acetonide OR Fluocinonide OR Fluocortolone OR Fluorometholone OR Fluprednisolone OR Flurandrenolone OR Melengestrol Acetate OR Methylprednisolone OR Paramethasone OR Prednisolone OR Prednisone OR Triamcinolone OR Triamcinolone Acetonide</p> <p>#8 Steroid* OR glucocorticoid*</p> <p>#9 (#5 OR #6 OR #7 OR #8)</p> <p>#10 (#4 AND #9)</p>	<p>#1 transtympanic* [tiab] OR intratympanic* [tiab] OR tympanic [tiab] OR topical* [tiab] OR local* [tiab] OR ITS [tiab] OR "MIDDLE EAR" [tiab] OR "INNER EAR" [tiab]</p> <p>#2 "Ear" [Mesh] OR "Drug Administration Routes" [Mesh]</p> <p>#3 #1 OR #2</p> <p>#4 "Steroids" [Mesh] OR "Glucocorticoids" [Mesh]</p> <p>#5 Beclomethasone [tiab] OR Betamethasone [tiab] OR Budesonide [tiab] OR Clobetasol [tiab] OR Desoximetasone [tiab] OR Dexamethasone [tiab] OR Dexamethasone Isonicotinate [tiab] OR Diflucortolone [tiab] OR Flumethasone [tiab] OR Fluocinolone Acetonide [tiab] OR Fluocinonide [tiab] OR Fluocortolone [tiab] OR Fluorometholone [tiab] OR Fluprednisolone [tiab] OR Flurandrenolone [tiab] OR Melengestrol Acetate [tiab] OR Methylprednisolone [tiab] OR Paramethasone [tiab] OR Prednisolone [tiab] OR Prednisone [tiab] OR Triamcinolone [tiab] OR Triamcinolone Acetonide [tiab] OR Steroid* [tiab] OR glucocorticoid* [tiab]</p> <p>#6 #4 OR #5</p> <p>#7 "Endolymphatic Hydrops"</p>	<p>1 (transtympanic* or intratympanic* or tympanic or topical* or local* or ITS or (MIDDLE adj EAR) or (INNER adj EAR)).tw.</p> <p>2 exp drug administration/</p> <p>3 1 or 2</p> <p>4 exp steroid/</p> <p>5 exp glucocorticoid/</p> <p>6 (Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Dexamethasone Isonicotinate or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Triamcinolone Acetonide or Steroid* or glucocorticoid*).tw.</p> <p>7 4 or 5 or 6</p> <p>8 3 and 7</p> <p>9 exp Meniere disease/</p> <p>10 (meniere* or (endolymphatic and hydrops) or (labyrinth and hydrops) or (labyrinth and syndrome) or (aural and vertigo) or (labyrinth and vertigo) or</p>	<p>S1 TX (transtympanic* or intratympanic* or tympanic or topical* or local* or ITS or (MIDDLE adj EAR) or (INNER adj EAR))</p> <p>S2 MH ear</p> <p>S3 MH drug administration routes</p> <p>S4 S1 or S2 or S3</p> <p>S5 MH steroids OR glucocorticoids</p> <p>S6 TX Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Dexamethasone Isonicotinate or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Triamcinolone Acetonide or Steroid* or glucocorticoid*</p> <p>S7 S5 or S6</p> <p>S8 S4 and S7</p> <p>S9 (MH "Meniere's Disease")</p> <p>S10 TX (meniere* or (endolymphatic and hydrops) or (labyrinth and hydrops) or (labyrinth and syndrome) or (aural and vertigo) or (labyrinth and vertigo) or</p>

(Continued)

<p>#11 MeSH descriptor Endolymphatic Hydrops explode all trees            #12 meniere*            #13 endolymphatic near hydrops            #14 labyrinth near hydrops            #15 labyrinth near syndrome            #16 aural near vertigo            #17 labyrinth near vertigo            #18 cochlea near hydrops            #19 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)            #20 (#10 AND #19)</p>	<p>[Mesh] OR meniere* [tiab] OR (endolymphatic [tiab] AND hydrops [tiab]) OR (labyrinth [tiab] AND hydrops [tiab]) OR (labyrinth [tiab] AND syndrome [tiab]) OR (aural [tiab] AND vertigo [tiab]) OR (labyrinth [tiab] AND vertigo [tiab]) OR (cochlea [tiab] AND hydrops [tiab])            #8 #3 AND #6 AND #7</p>	<p>(cochlea and hydrops)).tw.            11 9 or 10            12 8 and 11</p>	<p>and vertigo) or (cochlea and hydrops))            S11 S9 or S10            S12 S8 and S11</p>
<p><b>Web of Science/BIOSIS Previews (Web of Knowledge)</b></p>	<p><b>Cochrane Ear Nose and Throat Disorders Group Trials Register (ProCite database)</b></p>	<p><b>CAB Abstracts (Ovid)</b></p>	<p><b>ICTRP</b></p>
<p>#1 TS=(transtympanic* or intratympanic* or tympanic or topical* or local* or ITS or (MIDDLE adj EAR) or (INNER adj EAR))            #2 TS=(Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Dexamethasone Isonicotinate or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocinolone or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Triamcinolone Acetonide or Steroid* or glucocorticoid*)            #3 TS=(meniere* or (endolymphatic and hydrops) or (labyrinth and hydrops) or (labyrinth and syndrome) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops))</p>	<p>(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 (transtympanic* OR intratympanic* OR tympanic OR topical* OR local* OR ITS OR (MIDDLE AND EAR) OR (INNER AND EAR) )</p>	<p>1 (transtympanic* or intratympanic* or tympanic or topical* or local* or ITS or (MIDDLE adj EAR) or (INNER adj EAR) ).tw.            2 exp glucocorticoid/            3 (Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Dexamethasone Isonicotinate or Diflucortolone or Flumethasone or Fluocinolone Acetonide or Fluocinolone or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone or Triamcinolone Acetonide or Steroid* or glucocorticoid*) .tw.            4 2 OR 3            5 1 AND 4            6 (meniere* or (endolymphatic and hydrops) or (labyrinth and</p>	<p>meniere* OR labyrinth* OR cochlea AND hydrops</p>

(Continued)

#4 #1 AND #2 AND #3		hydrops) or (labyrinth and syndrome) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).tw. 7 5 AND 6	
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## HISTORY

Protocol first published: Issue 5, 2010

Review first published: Issue 7, 2011

## CONTRIBUTIONS OF AUTHORS

JP: lead author, protocol development, design of search strategy, quality assessment, data extraction and analysis.

BW: protocol development, quality assessment, data extraction and analysis.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- None, Not specified.

### External sources

- None, Not specified.

## INDEX TERMS

**Medical Subject Headings (MeSH)**

Dexamethasone [\*administration & dosage]; Ear, Middle; Glucocorticoids [\*administration & dosage]; Meniere Disease [\*drug therapy]; Randomized Controlled Trials as Topic; Syndrome; Vertigo [drug therapy]

**MeSH check words**

Humans