ClinicalEvidence

Menière's disease

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ABSTRACT

INTRODUCTION: Menière's disease causes feelings of fullness or pressure in the ear, hearing loss, tinnitus, and recurrent bouts of vertigo, and mainly affects people aged 30–60 years. Menière's disease is at first progressive but fluctuating, and episodes can occur in clusters. Vertigo usually resolves eventually, but the hearing deteriorates and the tinnitus and pressure may persist regardless of treatment. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical questions: What are the effects of combination treatment (betahistine plus thiazide diuretic) to prevent attacks and delay disease progression of Menière's disease? What are the effects of intratympanic interventions to prevent attacks and delay disease progression of Menière's disease? What are the effects of non-drug interventions to prevent attacks and delay disease progression of Menière's disease? What are the effects of dietary interventions to prevent attacks and delay disease progression of Menière's disease? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 200 studies. After deduplication and removal of conference abstracts, 151 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 100 studies and the further review of 51 full publications. Of the 51 full articles evaluated, five systematic reviews and four RCTs were added at this update. We performed a GRADE evaluation for eight PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for seven interventions based on information about the effectiveness and safety of betahistine plus thiazide diuretic, caffeine restriction, intratympanic corticosteroids, intratympanic gentamicin, psychological support, salt restriction, and vestibular rehabilitation.

QUESTIONS

INTERVENTIONS

COMBINATION TREATMENT (BETAHISTINE PLUS THIAZIDE DIURETIC) TO PREVENT ATTACKS AND DELAY DISEASE PROGRESSION

Unknown effectiveness

INTRATYMPANIC INTERVENTIONS TO PREVENT ATTACKS AND DELAY DISEASE PROGRESSION

Likely to be beneficial

Unknown effectiveness

NON-DRUG INTERVENTIONS TO PREVENT ATTACKS AND DELAY DISEASE PROGRESSION

Unknown effectiveness

DIETARY INTERVENTIONS TO PREVENT ATTACKS AND DELAY DISEASE PROGRESSION

Unknown effectiveness

Key points

- Menière's disease causes fullness or pressure in the ear, hearing loss, tinnitus, and recurrent vertigo and mainly affects people aged 30–60 years.

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

  The unpredictable bouts of vertigo can be disabling.

  Between attacks, the balance is usually normal but the hearing loss and tinnitus usually persist.

  Vertigo usually resolves eventually, but hearing deteriorates and the tinnitus and pressure may persist regardless of treatment.

- The previous version of this overview examined treatments for acute attacks and interventions such as betahistine alone and diuretics alone to prevent acute attacks. This updated overview examines a further range of options to prevent attacks and delay disease progression.
- We searched for RCTs and systematic reviews of RCTs to identify what high-quality evidence was available to inform practice.
- Overall, the RCTs we found were small and of very limited quality, making it difficult to draw any robust conclusions. There is a need for further high-quality trials in this field, although the difficulties of undertaking studies in this area should not be underestimated.
- We found no RCTs on the effects of betahistine plus thiazide diuretics versus betahistine or thiazide diuretics alone.
- We found two small RCTs of 50 people in total comparing intratympanic gentamicin with placebo.

  The trials differed in terms of regimens used (including the method of administration), trial design, and quality, which precluded combining data. Both were in highly selected populations of people with unilateral Menière's disease in whom vertigo was a major or incapacitating symptom, and who had not responded to conservative treatment.

  We found limited evidence that intratympanic gentamicin may improve vertigo and sensation of aural fullness compared with placebo, but evidence was very weak.

  We don't know about severity of tinnitus, functional impairment, or quality of life.

  One RCT found a higher absolute increase in hearing loss with gentamicin, but did not test the significance of differences between groups.
- We found two small RCTs of 42 people in total comparing intratympanic dexamethasone with placebo.

  We found limited evidence that intratympanic dexamethasone was more effective than placebo at improving vertigo and functional impairment at 2 years. However, this was based on one RCT of 22 people, only 11 of whom received intratympanic dexamethasone, and evidence was very weak.

  We don't know about hearing, severity of tinnitus, or quality of life.

  The two RCTs came to slightly different overall conclusions. They differed in trial design (one was a crossover RCT), method of dexamethasone administration, and trial duration (2 years versus 3 weeks).
- We found no good-quality evidence on the effects of psychological support or vestibular rehabilitation.
- We found no RCTs comparing salt restriction with no salt restriction or comparing caffeine restriction with no caffeine restriction.

Clinical context

GENERAL BACKGROUND

Menière's disease is a disabling and disheartening condition, with clusters of attacks coming without obvious precipitating factors and in some cases ruining lives. Because the cause of the condition is unknown, treatment is difficult and empirical.

FOCUS OF THE REVIEW

This overview assesses a range of treatments that are in common use. The focus of treatment is controlling the vertigo. Individuals may need to try different protocols to achieve control, which is usually possible by trialling different treatments or combinations of treatments. Surgical interventions (vestibular neurectomy, labyrinthectomy, or saccus decompression) are not discussed in this overview but will be considered at the next update.

COMMENTS ON EVIDENCE

Overall, the RCTs that we identified and added at this update were small and of limited methodological quality. Differences in the populations studied, the regimens employed, and trial design precluded the pooling of results. We found no RCT evidence on some interventions. Although further high-quality RCTs are needed to inform clinical practice, the difficulties in undertaking RCTs in this field should not be underestimated. It is difficult to draw robust conclusions from the RCTs, given the limited evidence available.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, January 2006, to July 2014. A back search from 1966 was performed for the new options added to the scope at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 200 studies. After deduplication and removal of conference abstracts, 151 records were screened for inclusion in the overview.

Appraisal of titles and abstracts led to the exclusion of 100 studies and the further review of 51 full publications. Of the 51 full articles evaluated, five systematic reviews and four RCTs were added at this update.

ADDITIONAL INFORMATION

The placebo effect of any form of active management on the symptom of vertigo is high (around 60%) and makes clinical trials very difficult to evaluate.

DEFINITION

Menière's disease is characterised by recurrent episodes of spontaneous, usually rotational vertigo, sensorineural hearing loss, tinnitus, and a feeling of fullness or pressure in the affected ear. It is a condition that frequently lasts for decades. It is usually unilateral but may be bilateral. Acute episodes can occur in clusters of about 6–11 a year, although remission may last many months or even years. [1] The diagnosis is made clinically. [2] It is important to distinguish Menière's disease from other types of vertigo that might occur independently with hearing loss and tinnitus, and respond differently to treatment (e.g., benign positional vertigo, acute labyrinthitis, migraine) and from acoustic neuromas. Even Prosper Menière, who described the condition in 1861, had great difficulty in distinguishing patients with migraine and deafness from those with his condition. Strict diagnostic criteria help to identify the condition. In this overview, we have applied the classification of the American Academy of Otolaryngology-Head and Neck Surgery to assess the diagnostic rigour used in RCTs (see table 1, p 17), [3] [4] [5] although the 'certain diagnosis' involving post-mortem examination is incorrect, as several conditions can cause the same anatomical changes as found in Menière's disease.

INCIDENCE/ PREVALENCE

Menière's disease is most common between the ages of 30 and 60 years, although younger people may be affected. [6] [7] In Europe, the incidence is about 50–200/100,000 per year. One survey of general practitioner records of 27,365 people in the UK in the 1950s found an incidence of 43 affected people in a 1-year period (157/100,000). [8] Diagnostic criteria were not defined in this survey. One survey of more than 8 million people in 1973 in Sweden found an incidence of 46/100,000 per year with diagnosis strictly based on the triad of vertigo, hearing loss, and tinnitus. [9] From smaller studies, the incidence appears to be lower in Japan (17/100,000, based on national surveys of hospital attendances in 1977, 1982, and 1990) [7] and in Uganda. [10]

AETIOLOGY/ RISK FACTORS

Menière's disease is associated with anatomical changes in the inner ear: so-called endolymphatic hydrops. The volume of the endolymph, which fills the membranous labyrinth, increases while the volume of the perilymph, which surrounds the membranous labyrinth and fills the bony labyrinth, decreases. However, hydrops occurs in many other conditions associated with hearing loss, and there is no known cause for this condition. [11] Specific disorders associated with hydrops (such as temporal bone fracture, syphilis, end-stage otosclerosis, acoustic neuromas) can produce symptoms similar to those of Menière's disease. Other conditions without anatomical changes in the inner ear can also produce symptoms similar to Menière's (such as migraine and the very rare Cogan's syndrome). Personality features have long been assumed to be part of the Menière's make-up with increased obsessionality scores, but whether this is the result of the condition or a contributor to its cause is not clear.

PROGNOSIS

Menière's disease is at first progressive but fluctuates unpredictably. It is difficult to distinguish natural resolution from the effects of treatment. Significant improvement in vertigo is usually seen in the placebo arm of RCTs, [12] [13] in some cases approximately 60%. [14] [15] Acute attacks of vertigo often increase in frequency during the first few years after presentation and then decrease in frequency in association with sustained deterioration in hearing. [6] In most people, vertiginous episodes eventually cease completely. [16] In one 20-year cohort study in 34 people, 28 (82%) people had at least moderate-to-severe hearing loss (mean pure tone hearing loss >50 dB) and 16 (47%) developed bilateral disease. [1] Symptoms other than hearing loss improve in 60%–80% of people irrespective of treatment. [17] These features bedevil robust clinical trials as power is almost impossible to achieve given the low incidence of the condition. Good clinical trials should be planned over several years to take into account the natural fluctuations of the condition, so compliance with the studies can be low.

AIMS OF INTERVENTION

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

OUTCOMES

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

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date July 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to July 2014, Embase 1980 to July 2014, The Cochrane Database of Systematic Reviews 2014, issue 7 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing 20 or more individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of treatments for acute attacks of Menière's disease? What are the effects of interventions to prevent attacks and delay disease progression of Menière's disease? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 18). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of combination treatment (betahistine plus thiazide diuretic) to prevent attacks and delay disease progression of Menière's disease?**

OPTION **BETAHISTINE PLUS THIAZIDE DIURETIC VERSUS BETAHISTINE OR THIAZIDE DIURETIC ALONE** New

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found no direct information from RCTs about the effects of betahistine plus thiazide diuretics versus betahistine or thiazide diuretic alone in preventing attacks or delaying disease progression in people with Menière's disease.

Benefits and harms

Betahistine plus thiazide diuretic versus betahistine alone:

We found no systematic reviews or RCTs.

Betahistine plus thiazide diuretic versus thiazide diuretic alone:

We found no systematic reviews or RCTs.

Comment: The extreme sensitivity of the hearing and balance sensors relies mainly on the electrochemical composition of the endolymph — the fluid that surrounds the stereocilia of the cochlear and vestibular hair cells. There is a very high potassium and low sodium concentration in this fluid, and in the cochlea a high positive (80 mV) potential. Deflection of the stereocilia by sound or head movement results in ion channels opening in the stereocilia and potassium ions flooding down their electrochemical gradient into the hair cell body, which depolarises and generates the acoustic or vestibular nerve impulses. The homeostasis of the endolymph is maintained by the stria vascularis in the cochlea and the dark cell regions in the vestibular labyrinth. It is assumed that failure of these structures, for whatever reason, results in the fluctuating and initially reversible nature of the condition. Eventually, damage occurs and there can be permanent loss and reduction of hearing and vestibular function. The causes of the fluctuations are unknown, and many suggestions have been made. The stria vascularis has a very extensive blood supply and a microstructure much like the renal tubules, hence the rationale for the use of betahistine, which is supposed to enhance the blood supply, and thiazide diuretics, which are meant to normalise the endolymph. Salt and caffeine restrictions are also postulated to act by stabilising the endolymph.

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

OPTION INTRATYMPANIC GENTAMICIN New

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found two small RCTs of 50 people in total. The RCTs differed both in terms of the regimens used and in trial design and quality. This precluded the pooling of results.
- The two RCTs also employed different methods of intratympanic gentamicin administration.
- Both RCTs included highly selected populations with unilateral Menière's disease, in whom vertigo was a major or incapacitating symptom and who had not responded to medical or other conservative treatment.
- The RCTs found limited evidence that intratympanic gentamicin may reduce vertigo symptoms and the sensation of aural fullness compared with placebo. However, evidence was very weak.
- We don't know whether intratympanic gentamicin is more effective than placebo at improving the severity of tinnitus.
- One small RCT found higher absolute levels of hearing loss with intratympanic gentamicin compared with placebo, but did not test the significance of differences between groups, and evidence was weak.
- We found no good evidence on functional impairment, quality of life, or adverse events other than those on hearing.

Benefits and harms

Intratympanic gentamicin versus placebo/sham treatment/no treatment/usual care:

We found two systematic reviews (search dates 2010; [18] and 2011 [19]), which included the same two double-blind placebo-controlled RCTs. [14] [15] The first review did not pool the data from the RCTs because of heterogeneity (see Further information on studies). [18] The second review pooled data for the RCTs with observational studies. [19] We have, therefore, reported the RCTs from their original reports. Both studies included people diagnosed according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria. One RCT (22 people) included people with unilateral active Menière's disease in whom conservative/medical treatment (not further defined) had proven unsuccessful for at least 6 months, and who had incapacitating vertigo attacks occurring at least monthly and recorded for 6 months. [14] Exclusion criteria included contralateral otological pathology and ipsilateral middle ear pathology. The other RCT (28 people) included participants with unilateral Menière's disease, in whom treatment with betahistine had proved unsuccessful. [15] It excluded people in whom the ear to be treated was the better hearing ear, the person's most annoying complaint had to be vertigo, and electronystagmography had to show a caloric response. The regimens used in the two trials varied considerably (see Further information on studies).

Frequency and severity of acute attacks of vertigo

Intratympanic gentamicin compared with placebo Intratympanic gentamicin may be more effective than placebo at improving vertigo in highly selected people with unilateral Menière's disease in whom vertigo is a major symptom and who had not previously responded to medical/conservative treatment. However, evidence was very weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency and severity of acute attacks of vertigo					
[14] RCT	22 people, mean age 58–59 years (range 34–74 years), unilateral Menière's disease with incapacitating vertigo attacks, conservative/medical treatment for 6 months unsuccessful In review [18] [19]	**Change in number of vertiginous attacks per year , from baseline to end of treatment** 74 to 0 with intratympanic gentamicin 25 to 11 with placebo The follow-up period varied between 6–28 months	Between-group significance not reported The RCT only reported on changes from baseline within each group (for gentamicin: P = 0.002; for placebo: P = 0.028) One review noted the difference between groups in attacks at baseline (see Further information on studies).		
[15] RCT	28 people, median age 53–55 years, unilateral Menière's disease, most annoying complaint vertigo, vestibular testing showed caloric response, treatment with betahistine unsuccessful In review [18] [19]	**Change in mean vertigo score (4-point scale where 0 = none and 3 = severe) , from baseline to 1 year** 2.1 to 0.5 with intratympanic gentamicin 2.0 to 1.8 with placebo Absolute results reported graphically	Reported as significant difference between groups P value not reported	○○○	intratympanic gentamicin

Hearing acuity

Intratympanic gentamicin compared with placebo We don't know how intratympanic gentamicin and placebo compare at reducing hearing loss at up to 1 year in highly selected people with unilateral Menière's disease in whom vertigo is a major symptom and who had not previously responded to medical/conservative treatment. Absolute levels of hearing loss were higher with gentamicin than placebo in one RCT, but the RCT did not test the significance of differences between groups, and evidence was weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hearing loss					
[14] RCT	22 people, mean age 58–59 years (range 34–74 years), unilateral Menière's disease with incapacitating vertigo attacks, conservative/medical treatment for 6 months unsuccessful In review [18] [19]	**Change in extended Fletcher index (average of the pure tone audiogram thresholds at 0.5, 1.0, 2.0, and 4.0 kHz) , from baseline to end of treatment** 60.0 dB HL to 54.0 dB HL with intratympanic gentamicin 53.0 dB HL to 58.8 dB HL with placebo The follow-up period varied between 6 and 28 months	Between-group significance not reported The RCT only reported changes from baseline within each group (for gentamicin: P = 0.17; for placebo: P = 0.24)		
[15] RCT	28 people, median age 53–55 years, unilateral Menière's disease, most annoying complaint vertigo, vestibular testing showed caloric re-	**Increase in hearing loss (extended Fletcher index [eFi: average of losses at 0.5, 1, 2, and 4 kHz]) , from baseline to 1 year** 8.1 dB with intratympanic gentamicin 0.0 dB with placebo	Between-group significance not reported One review noted that 1 person had a hearing loss of 60 dB, 2 people had a loss of 20 dB, and 1 person had a loss of 30 dB with gentamicin, and increases of this magnitude did not occur with		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	sponse, treatment with betahistine unsuccessful In review [18] [19]	Absolute results reported graphically	placebo (see Further information on studies) One person experienced an improvement of 20 dB in the gentamicin group (see Further information on studies)		

Severity of tinnitus

Intratympanic gentamicin compared with placebo We don't know whether intratympanic gentamicin is more effective than placebo at reducing tinnitus at 1 year in highly selected people with unilateral Menière's disease in whom vertigo is a major symptom and who had not previously responded to treatment with betahistine (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of tinnitus					
[15] RCT	28 people, median age 53–55 years, unilateral Menière's disease, most annoying complaint vertigo, vestibular testing showed caloric response, treatment with betahistine unsuccessful In review [18] [19]	**Change in mean tinnitus severity score (4-point scale where 0 = none and 3 = severe), from baseline to 1 year** 2.5 to 2.3 with intratympanic gentamicin 2.4 to 2.2 with placebo Absolute results reported graphically	Reported as "the therapy did not significantly change the scores" P value not reported		

No data from the following reference on this outcome. [14]

Sensation of aural fullness

Intratympanic gentamicin compared with placebo Intratympanic gentamicin may be more effective than placebo at reducing mean aural fullness severity scores at 1 year in highly selected people with unilateral Menière's disease in whom vertigo is a major symptom and who had not previously responded to treatment with betahistine (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Aural fullness severity					
[15] RCT	28 people, median age 53–55 years, unilateral Menière's disease, most annoying complaint vertigo, vestibular testing showed caloric response, treatment with betahistine unsuccessful In review [18] [19]	**Change in mean aural fullness severity score (4-point scale where 0 = none and 3 = severe), from baseline to 1 year** 1.7 to 0.9 with intratympanic gentamicin 1.8 to 1.8 with placebo Absolute results reported graphically	Reported as significant difference between groups P value not reported	○○○	intratympanic gentamicin

No data from the following reference on this outcome. [14]

Functional impairment

No data from the following reference on this outcome. [14] [15]

Quality of life

No data from the following reference on this outcome. [14] [15]

Adverse effects

No data from the following reference on this outcome. [14] [15]

Further information on studies

[18] *Heterogeneity* The first review concluded that clinical heterogeneity precluded pooling results from the two RCTs. This included the number of injections given, the interval between injections, the amount of gentamicin used, the outcomes reported, and methodological heterogeneity in trial design and quality.

[18] *Regimens* The review reported that in one RCT (22 people) [14] the solution was injected using a paracentesis technique and no grommet was inserted. Applications were repeated every 6 weeks until control of symptoms or one of the stop criteria was reached (including cumulative dose of gentamicin). It reported that this meant that people received a different number of injections (either of placebo or of gentamicin) within the two groups, and follow-up varied between participants (between 6 and 28 months). The second RCT (28 people) [15] used a middle ear ventilation tube placed 4 weeks before the start of injections. A total of four injections given weekly over 4 weeks were given. The follow-up period was 1 year.

[18] *Methods* Adequate sequence generation was reported as unclear in both RCTs. The review reported that the follow-up period in one RCT (from a minimum of 6 months) seemed insufficient, and that the protocol of repeated injections could introduce bias. It noted that there was a difference in the mean number of vertiginous attacks per year at baseline between the groups (74 in gentamicin group *v* 25 in placebo group). The review contacted the original trial author, who stated that the difference either before or after correction for the outlying value was not statistically significant, implying balanced randomisation. However, the review further noted that there may have been inadequate statistical power to detect clinically significant differences and a type III error occurred. The review noted that the follow-up in the other RCT (28 people) was 1 year, whereas the follow-up period recommended by the AAO-HNS is 2 years. Overall, it reported that the study that reported the largest effect was considered of poorer methodological quality than the other trial, but the higher-quality study had only 1 year of follow-up.

[18] *Hearing loss* The review noted that one RCT stated "hearing was reported unchanged by all subjects, i.e., no deafness or significant hearing loss occurred" while in the other RCT, average hearing loss was 8.1 dB with gentamicin versus 0.0 dB with placebo (P value not reported) and there were four people (25%) with hearing loss of over 15 dB in the gentamicin group, one of whom had a hearing loss of 60 dB.

Comment: The rationale for using intratympanic gentamicin is that the aminoglycoside antibiotics all have a damaging effect on the inner ear, with gentamicin preferentially damaging the vestibular hair cells rather than the auditory hair cells in the cochlea. The problem is getting the gentamicin into the fluids in the labyrinth, and this relies on diffusion through the round window membrane and the annular ligament around the stapes footplate after injection into the middle ear. Drug delivery is not controlled, and the results are likely to be variable. However, many specialists use this treatment and continue until the caloric responses from the inner ear are abolished. Unfortunately, this management has not been adequately assessed; however, in the treatment arm of the trial in one study, [14] the number of vertigo episodes fell dramatically.

Clinical guide

Failure of conventional medical treatment with betahistine and/or a thiazide diuretic along with the other forms of management often lead clinicians to suggest intratympanic gentamicin. This is an

invasive treatment, and it is possible that the placebo effect is enhanced; however, intratympanic gentamicin does have a logical basis in its application.

OPTION INTRATYMPANIC CORTICOSTEROIDS New

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found two small RCTs of 42 people in total. The RCTs differed in terms of regimens used, participants included, and methodological quality and design (one was a crossover RCT). They also employed different methods of intratympanic corticosteroid administration. One trial reported on outcomes at 2 years; the other only at 3 weeks. The two RCTs came to slightly different conclusions.
- We found limited evidence that intratympanic dexamethasone may improve vertigo symptoms and functional impairment compared with placebo at 2 years. However, this was based on one small RCT of 22 people, only 11 of whom received intratympanic dexamethasone, and evidence was very weak.
- We don't know about other symptoms such as hearing or severity of tinnitus.
- We found no good evidence on sensation of aural fullness, quality of life, or adverse effects.

Benefits and harms

Intratympanic corticosteroids versus placebo/sham treatment/no treatment/usual care:

We found two systematic reviews (search date 2011; [20] search date 2009 [21]), which found two RCTs between them, [22] [23] and we found one subsequent RCT. [24] The first double-blind RCT compared intratympanic dexamethasone with placebo in 24 people with unilateral Menière's disease as defined by AAO-HNS criteria who had previously failed to respond to 6 months of "conventional treatment" (described as restricted caffeine and salt, vasodilator, and diuretic, without any relief of vertigo attacks). [22] All participants were classified as Shea stage III (hearing loss for all tones, poor speech discrimination, but fullness, dizzy spells, and tinnitus are the main complaints). One injection per day was given for 5 consecutive days to the affected ear. The second crossover RCT compared intratympanic dexamethasone with placebo. [23] It included people with definite or probable unilateral Menière's disease by AAO-HNS criteria, the primary symptoms of participants were hearing loss, tinnitus, and aural fullness (Shea stage IV), and no participant was disabled by episodic vertigo. Participants were given a tympanostomy, and one injection per day was given for 3 consecutive days to the affected ear. We have only reported pre-crossover results from this RCT where available (see Further information on studies). The subsequent RCT compared two different doses of sustained-release dexamethasone formulation (OTO-104) with placebo in people with unilateral Menière's disease. [24] However, this RCT did not meet the inclusion criteria for this *BMJ Clinical Evidence* overview (see Comment).

Frequency and severity of acute attacks of vertigo

Intratympanic dexamethasone compared with placebo Intratympanic dexamethasone may be more effective than placebo at improving vertigo attacks at 2 years in people with unilateral Menière's disease who had previously failed to respond to medical treatment over 6 months. However, evidence was very weak (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of vertigo spells					
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Proportion of people achieving complete control of vertigo spells (AAO-HNS) , 2 years** 9/11 (82%) with intratympanic dexamethasone 4/7 (57%) with placebo 18 people included in analysis	Statistical analysis unclear		
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Mean vertigo subjective improvement (measured by scale 0–10 where 0 = no change and 10 = 100% improvement) , 2 years** 90% with intratympanic dexamethasone 57% with placebo 18 people included in analysis	P <0.001	○○○	intratympanic dexamethasone

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Change in mean Dizziness Handicap Inventory score (physical, emotional, and functional subsets) , from baseline to 2 years** 68.7 to 8.3 with intratympanic dexamethasone 65 to 23.7 with placebo 18 people included in analysis	P <0.008	○○○	intratympanic dexamethasone

Hearing acuity

Intratympanic dexamethasone compared with placebo We don't know whether intratympanic dexamethasone is more effective than placebo at reducing hearing loss at 3 weeks to 2 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hearing loss					
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Change in pure tone average , from baseline to 2 years** 55.7 to 53.4 dB with intratympanic dexamethasone 56.6 to 56 dB with placebo 18 people included in analysis	Statistical analysis unclear		
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Mean hearing loss subjective improvement (measured by 0–10 scale where 0 = no change and 10 = 100% improvement) , 2 years** 35% with intratympanic dexamethasone 10% with placebo 18 people included in analysis	P <0.001	○○○	intratympanic dexamethasone
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Change in mean speech discrimination score , baseline to 2 years** 68.5% to 66.7% with intratympanic dexamethasone 61.2% to 56.5% with placebo 18 people included in analysis	Statistical analysis unclear		
[23] RCT **Crossover design**	20 people, aged 21 years or older, with unilateral Menière's disease (definite or probable [defined by AAO-HNS]), no participant disabled by vertigo In review [21]	**Change in pure tone average , from baseline to 3 weeks** 48.4 dB to 50.5 dB with intratympanic dexamethasone 44.9 dB to 46.8 dB with placebo Pre-crossover data	P value not reported		
[23] RCT **Crossover design**	20 people, aged 21 years or older, with unilateral Menière's disease (definite or probable – defined by	**Change in speech discrimination score , from baseline to 3 weeks** 64.4% to 68.0% with intratympanic dexamethasone	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	AAO-HNS), no participant disabled by vertigo In review [21]	76.6% to 66.3% with placebo Pre-crossover data 16 people in this analysis			

Severity of tinnitus

Intratympanic dexamethasone compared with placebo We don't know whether intratympanic dexamethasone is more effective than placebo at improving severity of tinnitus at 3 weeks to 2 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of tinnitus					
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Change in mean Tinnitus Handicap Inventory (THI) score (functional, emotional, and catastrophic subsets) , from baseline to 2 years** 61 to 22.3 with intratympanic dexamethasone 56.9 to 15.7 with placebo 18 people in this analysis	Reported as not significant P value not reported	⟷	Not significant
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Change in mean tinnitus severity , from baseline to 2 years** 3.2 to 1.6 with intratympanic dexamethasone 3 to 1.2 with placebo 18 people in this analysis	P value not reported		
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Proportion of people achieving Grade 1 (grading of tinnitus severity; THI 0–16) , 2 years** 8/11 (72%) with intratympanic dexamethasone 6/7 (85%) with placebo 18 people in this analysis	P value not reported		
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**Mean tinnitus and aural subjective improvement , 2 years** 48% with intratympanic dexamethasone 20% with placebo 18 people in this analysis	P <0.005 One review noted that it was unclear whether this outcome was for tinnitus, aural fullness, or both (see Further information on studies)	○○○	intratympanic dexamethasone
[23] RCT **Crossover design**	20 people, aged 21 years or older with unilateral Menière's disease (definite or probable [defined by AAO-HNS]), no participant disabled by vertigo In review [21]	**Change in Tinnitus Handicap Inventory (THI) score , from baseline to 3 weeks** 44.2 to 44.1 with intratympanic dexamethasone 32.3 to 29.5 with placebo Pre-crossover data	P value not reported		
[23]	20 people, aged 21 years or older with	**Change in tinnitus severity (Florida Ear and Sinus Centre**	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
RCT **Crossover design**	unilateral Menière's disease (definite or probable – defined by AAO–HNS), no participant disabled by vertigo In review [21]	**Survey) , from baseline to 3 weeks** 7.0 to 6.6 with intratympanic dexamethasone 6.9 to 7.4 with placebo Pre-crossover data			

Sensation of aural fullness

No data from the following reference on this outcome. [22] [23]

Functional impairment

Intratympanic dexamethasone compared with placebo Intratympanic dexamethasone may be more effective than placebo at increasing the proportion of people achieving functional level 1 (AAO–HNS Functional level scale) at 2 years in people with unilateral Menière's disease who had previously failed to respond to medical treatment over 6 months. However, evidence was weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Functional improvement					
[22] RCT	22 people, mean age 50 years (range 28–77 years), unilateral Menière's disease, failed to respond to conventional treatment In review [20] [21]	**People achieving functional level 1 (AAO–HNS Functional level scale, 1–6 where 1 = dizziness has no effect on activities and not changed plans or activities to accommodate) , 2 years** 10/11 (90%) with intratympanic dexamethasone 3/7 (42%) with placebo 18 people in this analysis	P <0.001	○○○	intratympanic dexamethasone

Quality of life

No data from the following reference on this outcome. [22] [23]

Adverse effects

No data from the following reference on this outcome. [22] [23]

Further information on studies

[20] [22] *Methods* The review [20] excluded the cross-over RCT [23] as pre-crossover data were not available. The authors of the review contacted the trial authors of the included RCT [22] for further clarifications regarding other possible publications of the trial and to resolve ambiguities on data, but did not receive a response. The review noted

that the methods to achieve randomisation, allocation concealment, or blinding were not described. [20] In the dexamethasone group, all 11 people were analysed at 2 years. In the placebo group, four people were classed as treatment failures before 2 years, and one further person at 2 years, and these people were given an active treatment (including vestibular neuronectomy, endolymphatic sac decompression, dexamethasone inner ear perfusion). [22]

[23] The cross-over RCT initially enrolled 20 people to the study protocol to compare intratympanic dexamethasone with placebo. Each person underwent laser-assisted otoendoscopy, and a laser-assisted tympanostomy was created. The RCT also reported that, additionally, any obstructing bands or adhesions overlying the round window membrane were removed with a small pick. Three people (15%) failed to return for the 'second arm' of the study. The RCT reported that 10 people were randomised to receive corticosteroid first and seven people to receive placebo first. In addition, 15 people (60%) were reached for the final telephone interview. The groups were crossed over after 3 weeks; it was unclear whether there was any wash-out period, and the laser-assisted otoendoscopy procedure was not repeated at cross-over. Both reviews noted that the final results (post-crossover) of this RCT could be a carry-over from the first treatment period. [20] [21] Overall, taking into account post-crossover results, the RCT concluded that the intratympanic administration of dexamethasone showed no benefit over placebo for hearing loss or tinnitus in people with unilateral Menière's disease (Shea stage IV). However, the limitations of this trial should be noted.

Comment: The subsequent RCT compared two different doses of OTO-104 (a sustained-release dexamethasone formulation) with placebo given as a single injection. [24] Between 13% and 29% of people in the three groups had received intratympanic corticosteroid injections previously. Initially, people were allocated on a 2:1 basis to lower-dose intratympanic dexamethasone (14 people) or placebo (7 people). After a safety evaluation, "the high dose cohort was open to enrolment" and the remaining participants seem to have been allocated to higher-dose dexamethasone or placebo. However, the RCT did not present results separately for the two trials (pooled data for the placebo group). We have, therefore, not reported these data further.

Clinical guide
The proposed mechanism of action of intratympanic corticosteroid relies principally on the glucocorticoid effects of these drugs, as the mineralocorticoid effect, which could alter the sodium/potassium balance of the endolymph, is minimal or zero in the case of dexamethasone. This poses the question as to what is the inflammatory process or immune reaction that is present only in the affected ear? An alternative is that the intratympanic injection itself is acting as a powerful placebo, hence the lack of clear-cut benefit over controls.

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

OPTION PSYCHOLOGICAL SUPPORT

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found no clinically important results from RCTs comparing the effects of psychological support with placebo/sham/no treatment/usual care in preventing attacks or delaying disease progression in people with Menière's disease.

Benefits and harms

Psychological support versus placebo/sham treatment/no treatment/usual care:

We found no systematic review or RCTs.

Comment: In this option we have searched for RCTs of psychological support, including those on cognitive behavioural therapy (CBT) and mindfulness.

Symptomatic improvement is seen with all treatments for Menière's disease, including placebo [17] [25] or being put on a waiting list for surgery. [26] Such improvements may be attributed to the psy-

chological support of receiving treatment but have not been distinguished from improvements attributable to the natural history of Menière's disease.

Clinical guide
Patients with debilitating Menière's disease often have moderate or even severe psychological problems because of the insecurity of not knowing when attacks can occur (so that planning normal activities becomes impossible), they may lose self-confidence, have difficulty hearing, and the intrusive tinnitus can become overwhelming. Psychological support with CBT can be helpful but is limited by the fluctuating nature of the condition, which, when a new and severe attack occurs out of the blue despite all the best care, is devastating to individuals who thought they were on the track to recovery.

OPTION VESTIBULAR REHABILITATION

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found no clinically important results from RCTs comparing the effects of vestibular rehabilitation with placebo/sham/no treatment/usual care in preventing attacks or delaying disease progression in people with Menière's disease. However, evidence from unblinded studies suggests that the more support individuals have, the better they feel.

Benefits and harms

Vestibular rehabilitation versus placebo/sham treatment/no treatment/usual care:

We found one systematic review (search date 2010), [27] which evaluated vestibular rehabilitation in people with peripheral vestibular dysfunction. The review included one RCT with people with Menière's disease. [28] We also found one subsequent RCT. [29] Both RCTs were unblinded and, therefore, do not meet the inclusion criteria for this *BMJ Clinical Evidence* overview (see Comment).

Comment: The first RCT (360 people with Menière's disease, non-acute phase, volunteer sample from self-help group) compared a vestibular rehabilitation self-management booklet (including exercises), a symptom control booklet (using applied relaxation and other strategies), and a waiting-list control. [28] At 3 and 6 months there was a significant improvement in subjective health in the two intervention groups compared with the control group, with similar results reported for the two interventions. The second RCT (44 people with unilateral or bilateral disease) compared a virtual reality-based vestibular rehabilitation programme for people with Menière's disease (including stimulus-enriched exercises plus betahistine and dietary recommendations) with control (betahistine and dietary recommendations). [29] Patients who received the virtual reality exercises had significantly lower scores in Dizziness Handicap Inventory (DHI) and dizziness visual analogue scale, and significantly greater limit of stability areas compared with the control group. These studies suggest that the more support individuals have, the better they feel.

Clinical guide
Vestibular rehabilitation is a complex subject with many levels of interaction in the balance system. For a single event that results in a complete loss of the function of one inner ear, the Cawthorne-Cooksey exercises are applicable and can be beneficial. Cawthorne-Cooksey exercises do rely on stable function in both ears; therefore, if one ear has fluctuating vestibular function (as occurs in Menière's disease) then this rehabilitation regime is problematic. However, individuals distressed by 'out of the blue' symptoms can naturally develop hyperventilation syndromes and panic attacks, which will also make them feel dizzy. Caring, focused vestibular rehabilitation is part of the support system for people disabled by Menière's disease.

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

OPTION SALT RESTRICTION New

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found no clinically important results from RCTs comparing the effects of salt restriction with no salt restriction in preventing attacks or delaying disease progression in people with Menière's disease.

Benefits and harms

Salt restriction versus no salt restriction/no treatment/usual care:

We found no systematic review or RCTs.

Comment: It has been suggested that a low-salt diet reduces endolymphatic pressure in endolymphatic hydrops, [30] but we found no evidence from RCTs to support or refute this suggestion. Additionally, there is no good evidence that endolymphatic pressure is increased in Menière's disease. There may be alterations in osmotic pressure in the endolymph that result in fluid balance shifts to restore homeostasis, with consequent anatomical changes that are called hydrops. While salt overdose is generally held as not good for people, there does not seem to be any evidence that severe salt restriction has any benefit, as the kidneys simply respond to maintain normal salt levels. The renal system appears to be very good at restricting sodium loss but not so good at excreting overload. Major salt restriction is advocated by some, but this is based on unsound science.

OPTION CAFFEINE RESTRICTION New

- For GRADE evaluation of interventions for Menière's disease, see table, p 18 .
- We found no clinically important results from RCTs comparing the effects of caffeine restriction with no caffeine restriction in preventing attacks or delaying disease progression in people with Menière's disease.

Benefits and harms

Caffeine restriction versus no caffeine restriction/no treatment/usual care:

We found no systematic review or RCTs.

Comment: Overload with caffeine can make anyone feel unsteady, so moderation in the intake of caffeine is generally a good idea. However, there does not seem to be any good evidence that caffeine restriction is useful. It is frequently suggested in medical literature that, where a feature worsens a condition, the opposite will improve the condition. However, often this suggestion does not stand up to examination, and this is certainly the case in Menière's disease.

GLOSSARY

Cogan's syndrome Episodic vertigo of the Menière's type, hearing loss, and interstitial keratitis, without syphilis. [5]

Vestibular rehabilitation Involves a series of exercises intended to improve the sense of balance through controlled movements of the head and body. [31] It is usually recommended for stable vestibular disorders. [32]

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Betahistine plus thiazide diuretic versus betahistine or thiazide alone New option. We found no RCTs. Categorised as 'unknown effectiveness'.

Intratympanic gentamicin New option. Two systematic reviews added, [18] [19] which include two RCTs. [14] [15] Categorised as 'likely to be beneficial'.

Intratympanic corticosteroids New option. Two systematic reviews added [20] [21] and two RCTs. [22] [23] One RCT added to the Comment section. [24] Categorised as 'unknown effectiveness'.

Salt restriction New option. We found no RCTs. Categorised as 'unknown effectiveness'.

Caffeine restriction New option. We found no RCTs. Categorised as 'unknown effectiveness'.

Vestibular rehabilitation One systematic review [27] and two RCTs [28] [29] added to the Comment section. Categorisation unchanged (unknown effectiveness).

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Disclaimer

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

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

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

GRADE **Evaluation of interventions for Menière's disease.**

Important outcomes	Frequency and severity of acute attacks of vertigo, Functional impairment, Hearing acuity, Quality of life, Sensation of aural fullness, Severity of tinnitus								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of intratympanic interventions to prevent attacks and delay disease progression of Menière's disease?									
2 (50) [14] [15]	Frequency and severity of acute attacks of vertigo	Intratympanic gentamicin versus placebo/sham treatment/no treatment/usual care	4	–3	0	–1	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, and sparse data; directness point deducted for clinical heterogeneity between RCTs
2 (50) [14] [15]	Hearing acuity	Intratympanic gentamicin versus placebo/sham treatment/no treatment/usual care	4	–3	0	–1	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, and sparse data; directness point deducted for clinical heterogeneity between RCTs
1 (28) [15]	Severity of tinnitus	Intratympanic gentamicin versus placebo/sham treatment/no treatment/usual care	4	–2	0	–1	0	Very low	Quality points deducted for weak methods and sparse data; directness point deducted for unclear statistical analysis between groups
1 (28) [15]	Sensation of aural fullness	Intratympanic gentamicin versus placebo/sham treatment/no treatment/usual care	4	–3	0	0	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, and sparse data
1 (18) [22]	Frequency and severity of acute attacks of vertigo	Intratympanic corticosteroids versus placebo/sham treatment/no treatment/usual care	4	–3	0	0	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, and sparse data
2 (38) [22] [23]	Hearing acuity	Intratympanic corticosteroids versus placebo/sham treatment/no treatment/usual care	4	–3	0	0	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, and sparse data
2 (38) [22] [23]	Severity of tinnitus	Intratympanic corticosteroids versus placebo/sham treatment/no treatment/usual care	4	–3	0	0	0	Very low	Quality points deducted for weak methods, incomplete reporting of results, and sparse data
1 (18) [22]	Functional impairment	Intratympanic corticosteroids versus placebo/sham treatment/no treatment/usual care	4	–2	0	0	0	Low	Quality points deducted for weak methods and sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.