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Ménière's Disease Treatment: A Patient-Centered Systematic Review

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Key Words
Ménière's disease · Idiopathic endolymphatic hydrops · Person-centred healthcare and medicine paradigm

Abstract
Ménière's disease is a disorder of the inner ear affecting hearing and balance to a varying degree. It is characterized by episodes of vertigo, low-pitched tinnitus, and hearing loss. There is currently no gold standard treatment for Ménière's disease. We conducted a systematic search of the Cochrane Database, as a high-quality source of evidence-based therapies, for reviews on the efficacy of etiological therapy or on Ménière's disease or its symptoms. Following recent positive experiences reported by other research teams, we decided to involve a patients' representative in the assessment and analysis of the evidence retrieved in the literature in order to achieve a more patient-centered evaluation of the therapies. Evidence confirms that an effective treatment of Ménière's disease is still missing, but recent discoveries on the microvascular etiology of Ménière's disease may be assimilated by new evidence-based therapeutic approaches.

Introduction

Ménière's disease (idiopathic endolymphatic hydrops) is a disorder of the inner ear that can affect hearing and balance to a varying degree. It is characterized by episodes of vertigo, low-pitched tinnitus, and hearing loss. The hearing loss is fluctuating rather than permanent, meaning that it comes and goes, alternating between ears for some time, and then it becomes permanent with no return to normal function. The disease is named after the French physician Prosper Ménière [Baloh, 2001] who in two articles published in 1861 [Menière, 1861; Ménière, 1861] first reported that vertigo was caused by inner ear disorders. Although celebrated public characters from the past probably suffered from this disease, most notably Charles Darwin [Hayman, 2009], Vincent Van Gogh [Arenberg et al., 1990], and Marilyn Monroe [Stephens and Mudry, 2012], this syndrome had attracted little attention. There have been never-ending controversies on the etiopathology of the disease and there is still a lack of effective therapeutic approaches after more than 150 years since the discovery of the syndrome: according to the NHS 'there is no single treatment for Ménière's disease, mainly because the exact cause is still unknown' (http://www.nhs.uk/Conditions/Menieres-disease/

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Pages/Treatment.aspx). The typical clinical triad of symptoms (recurrent vertigo, fluctuating sensorineural hearing loss, and tinnitus) is often pathognomonic, and diagnosis is based on criteria established in 1995 by the American Academy of Otolaryngology – Head and Neck Foundation [Katsarkas, 1996]. Symptoms that may be unilateral or bilateral [Clemmens and Ruckenstein, 2012] are caused by endolymphatic hydrops of the inner ear, while 75% of the patients with unilateral symptoms still present with bilateral endolymphatic hydrops [Pyykko et al., 2013]. A glycerol dehydration test and electrocochleography are the main diagnostic tests in current practice, while vestibular evoked myogenic potentials may be used for disease staging. Imaging techniques are not specific enough to make alone the diagnosis of Ménière's disease, although they may be necessary to exclude other pathologies. Recently developed 3D MRI protocols can delineate the perilymphatic/endolymphatic spaces of the inner ear and aid diagnosis [Vassiliou et al., 2011]. The reported prevalence rates for Ménière's syndrome range from 3.5 per 100,000 to 513 per 100,000. A recent study using health claims, including data from more than 60 million individuals in the US, found a prevalence of 190 per 100,000 with a female:male ratio of 1.89:1 [Alexander and Harris, 2010]. The prevalence of Ménière's disease in Northern European countries seems markedly high: approximately 430 cases per million are reported in Finland [Kotimaki et al., 1999] and 460 cases per million in Sweden [Stahle et al., 1978]. The prevalence of Ménière's syndrome increases with increasing age. In Italy, an incidence of 8.2 per million per year was estimated, but this is probably an underestimation [Celestino and Ralli, 1991]. Therefore, Ménière's disease should be considered as a 'rare disease' according to both the EU (http://ec.europa.eu/health/ph_information/documents/ev20040705_rd05_en.pdf) and the US (http://www.gpo.gov/fdsys/pkg/PLAW-107publ280/html/PLAW-107publ280.htm) definitions, which report incidences lower than 1 per 2,000 or less than 200,000 cases, respectively. The pathophysiology of the disease was, and still is, a matter of debate [Pfaltz, 1986], and many causal factors for Ménière's disease have been investigated: genetic factors [Fung et al., 2002; Semaan and Megerian, 2010] and hereditary factors [Hietikko et al., 2013], vascular [Yamagata et al., 1964] and environmental factors [Calabrese et al., 2010; Colletti et al., 2011; Hess et al., 1991; Roland et al., 2000; Vassiliou et al., 2011; Wienke and Janke, 2007], infections [DiBerardino et al., 2007; Miller et al., 2010], immunologic [Bovo et al., 2010; Derebery and Berliner, 2010; Krzeska-Malinowska et al., 2002; Paparella and Djalilian, 2002; Rauch et al., 1995; Tomiyama, 2003] and iatrogenic factors [Katahira et al., 2013; Pirodda et al., 2011; Takumida et al., 2008], and even psychological factors [Eagger et al., 1992]. None of these candidates seems to be necessary and sufficient to cause the disease. Frequently, Ménière's disease is associated with other degenerative diseases such as multiple sclerosis [Bovo et al., 2010; Spencer et al., 2002], Alzheimer's disease, autoimmune thyroiditis [Fattori et al., 2008], hyperinsulinemia [D'Avila and Lavinsky, 2005; Kirtane et al., 1984], migraine [Ibekwe et al., 2008], and Cogan syndrome [Gasparovic et al., 2011; Haynes et al., 1980].

Different therapies were proposed, some of them effective in certain patients or for certain symptoms, but the results are generally highly heterogeneous in the treated population. Because of these heterogeneous responses, it is extremely complicated for the Ménière's disease patient and for the physician to integrate and reach optimal care and treatment. Moreover, treatment should be tailored specifically and dynamically on the different symptoms and needs which the patients experience chronically (for example, tinnitus) or irregularly (for example, 'drop attacks', also known as otolithic crisis of Tumarkin). In this review, we summarize the state-of-the-art of the etiologic treatments for Ménière's disease and symptomatic treatments of vertigo and tinnitus according to the most recent evidence-based evaluations through systematic reviews by the Cochrane Group. We decided to include only Cochrane Systematic Reviews because of their high methodological quality [Jorgensen et al., 2006] and common and transparent criteria [Higgins and Green, 2011], although the underreporting of adverse events in the studies included in these reviews remains a major limiting factor when it comes to translating the findings of these reviews to patient-centered decision making (this is a common problem for all systematic reviews of interventions, not only for Cochrane Reviews) [Zorzela et al., 2014]. New therapeutic options, recent etiological research findings, and possible methodological improvements to overcome the current limits in the assessment and integration of the evidence on Ménière's disease or syndrome will be addressed in our discussion. In light of the positive effects recently reported by other authors [Gartlehner and Flamm, 2013] of engaging consumer and patient representatives in systematic reviews of the literature and patient-centered evaluations, we asked N.G., president of the Italian Ménière Disease Patients Association (AMMI) [Gaggioli, 2013], to actively participate in all the stages of the review process.

Methods

We searched the Cochrane Database of Systematic Reviews in the Cochrane Library for any reviews with 'Ménière' or 'idiopathic endolymphatic hydrops' and with 'tinnitus' or 'vertigo' in the title, abstract, or key word fields. The last search was conducted in June 2014. Authors, title, year, objectives, selection criteria, main results, and authors' conclusion were retrieved for each review that matched these inclusion criteria. Nineteen reviews matching our inclusion criteria were identified, but 4 were excluded already at the protocol stage. Therefore, 15 Cochrane Reviews were identified, 5 addressing the etiologic treatment of Ménière's disease and 10 addressing symptomatic therapy of Ménière's disease (9 on tinnitus and 1 on vertigo). Other references cited in the introduction and in the discussion chapters were retrieved through PubMed, Embase, Web of Science, Scopus, and Google Scholar.

Results

Cochrane Systematic Reviews of etiologic treatments for Ménière's disease or syndrome included diuretics [Burgess and Kundu, 2006], betahistine [James and Burton, 2001], intratympanic gentamicin [Pullens and van Benthem, 2011], intratympanic steroids [Phillips and Westerberg, 2011], and surgery [Pullens et al., 2013]. Cochrane Systematic Reviews of symptomatic tinnitus treatments of interest for Ménière's disease or syndrome included tinnitus retraining therapy [Phillips and McFerran, 2010], anticonvulsants [Hoekstra et al., 2011], sound therapy (masking) [Hobson et al., 2010], ginkgo biloba [Hilton et al., 2013], cognitive behavioral therapy (CBT) [Martinez-Devesa et al., 2010], repetitive transcranial magnetic stimulation (rTMS) [Meng et al., 2011], antidepressants [Baldo et al., 2012], hyperbaric oxygen therapy [Bennett et al., 2012], and amplification with hearing aids for patients with tinnitus and coexisting hearing loss [Hoare et al., 2014]. Cochrane Systematic Reviews of symptomatic vestibular treatments of interest for Ménière's disease or syndrome included vestibular rehabilitation [Hillier and McDonnell, 2011]. The results of our research are summarized in table 1 and 2.

According to the Cochrane Systematic Reviews on etiologic treatments of Ménière's disease, there is sufficient evidence of effectiveness only for intratympanic gentamicin which 'seems to be an effective treatment for vertigo complaints in Ménière's disease' [Pullens and van Benthem, 2011]. Only limited evidence supports the effectiveness of intratympanic steroids in patients with Ménière's disease [Phillips and Westerberg, 2011]. Finally, insufficient evidence of effectiveness was found for the following treatments of Ménière's disease: diuretics, betahistine, and endolymphatic sac surgery [Burgess and Kundu, 2006; James and Burton, 2001; Pullens et al., 2013]. Three of these reviews included only randomized controlled trials (RCTs) versus placebo, 2 included also quasi-randomized trials versus placebo, and 1 (intratympanic gentamicin) included also randomized or quasi-randomized trials versus other treatment.

According to the Cochrane Systematic Reviews on symptomatic treatments of tinnitus, there is sufficient evidence of effectiveness only for tinnitus retraining therapy [Phillips and McFerran, 2010]. Only limited evidence supports the effectiveness for tinnitus of sound therapy (masking), where 'studies failed to show strong evidence of the efficacy' [Hobson et al., 2010], of CBT, which induced 'significant improvement in depression score and quality of life suggesting that CBT has a positive effect on the management of tinnitus' [Martinez-Devesa et al., 2010], and of rTMS, where 'there is very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus' [Meng et al., 2011]. Limited evidence also supports the use of hearing aids in patients with tinnitus and coexisting hearing loss: 'there is currently no evidence to support or refute their use as a more routine intervention for tinnitus' [Hoare et al., 2014]. Insufficient evidence of effectiveness of treatments for tinnitus was found for anticonvulsants, ginkgo biloba, antidepressants, and hyperbaric oxygen therapy [Baldo et al., 2012; Bennett et al., 2012; Hilton et al., 2013; Hoekstra et al., 2011]. Three of these reviews included just RCTs versus placebo or sham, while 6 included also randomized and nonrandomized trials versus another treatment.

According to the only Cochrane Systematic Reviews on symptomatic treatments of vestibular dysfunction, there is sufficient evidence of effectiveness of vestibular rehabilitation as a 'safe, effective management for unilateral peripheral vestibular dysfunction, based on a number of high quality randomized controlled trials' [Hillier and McDonnell, 2011].

Discussion

After 58 years during which betahistine (which was in fact the first therapy proposed and utilized by Godlowski already in 1965) has been one of the most frequently prescribed drugs for Ménière's disease in Europe and the UK [Lacour et al., 2007; Smith et al., 2005], it is disturbing to read the conclusion of the Cochrane Review authors: 'there is insufficient evidence to say whether betahistine has any effect on Ménière's disease' [James

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Table 1. Cochrane Reviews on Ménière's disease (ethiological therapy)

First author: title, year of study (year of publication)	Objectives	Selection criteria	Main results	Authors' conclusions
Burgess: Diuretics for Ménière's disease or syndrome, 2006 (2006)	To assess the effect of diuretic treatment in patients with Ménière's disease.	RCTs of diuretic vs. placebo in Ménière's disease patients.	There were no trials of a high enough quality to meet the standard set for this review.	There is insufficient good evidence of the effect of diuretics on vertigo, hearing loss, tinnitus, or aural fullness in clearly defined Ménière's disease.
James: Betahistine for Ménière's disease or syndrome, 2001 (2001)	The objective of this review was to assess the effects of betahistine in people with Ménière's disease.	Randomized controlled studies of betahistine vs. placebo in Ménière's disease.	Seven trials involving 243 patients were included. No trial met the highest quality standard set by the review because of inadequate diagnostic criteria or methods, and none assessed the effect of betahistine on vertigo adequately. Most trials suggested a reduction of vertigo with betahistine, and some suggested a reduction in tinnitus, but all these effects may have been caused by bias in the methods. One trial with good methods showed no effect of betahistine on tinnitus compared with placebo in 35 patients. None of the trials showed any effect of betahistine on hearing loss. No serious adverse effects were found with betahistine.	There is insufficient evidence to say whether betahistine has any effect on Ménière's disease.
Pullens: Surgery for Ménière's disease, 2010 (2013)	To assess the effectiveness of surgical options for the treatment of Ménière's disease. All surgical interventions used in the treatment of Ménière's disease, either to alter the natural history of the disease or to abolish vestibular function, were considered for this review.	Randomized or quasi-randomized controlled studies of a surgical modality vs. a placebo therapy in Ménière's disease.	The only surgical intervention which had been evaluated in RCTs and met the inclusion criteria was endolymphatic sac surgery. We identified 2 randomized trials involving a total of 59 patients, 1 comparing endolymphatic sac surgery with ventilation tubes and 1 with simple mastoidectomy. Neither study reported any beneficial effect of surgery either in comparison to placebo surgery or grommet insertion.	The 2 trials included in this review provide insufficient evidence of the beneficial effect of endolymphatic sac surgery in Ménière's disease.
Pullens: Intratympanic gentamicin for Ménière's disease or syndrome, 2011 (2011)	To assess the effectiveness of intratympanic gentamicin in the treatment of vertigo in Ménière's disease.	All randomized or quasi-RCTs of intratympanic gentamicin vs. placebo, or vs. another treatment for Ménière's disease.	We identified 2 trials, involving 50 participants, which fulfilled the inclusion criteria. Both of these trials are prospective, double-blind, placebo-controlled randomized clinical trials on the effect of intratympanic gentamicin on vertigo complaints. After assessing the risk of bias of both studies, we concluded that 1 had a greater risk of bias and deemed the other to be of higher quality. Both of these trials found a significant reduction in vertigo complaints in the gentamicin group when compared to the placebo group. Due to clinical heterogeneity, we could not perform a meta-analysis. One study described an increase in hearing loss in 4 patients (25%) treated with gentamicin, while the other described no increase in hearing loss. No other adverse effects were noted by either study.	Based on the results of the 2 included studies, intratympanic gentamicin seems to be an effective treatment for vertigo complaints in Ménière's disease but carries a risk of hearing loss.
Phillips: Intratympanic steroids for Ménière's disease or syndrome, 2011 (2011)	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.	RCTs of intratympanic dexamethasone vs. placebo in patients with Ménière's disease.	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 vs. 42%), class (82 vs. 57%), change in Dizziness Handicap Inventory scores (60.4 vs. 41.3), and mean vertigo subjective improvement (90 vs. 57%). The treatment regime described by the authors involved daily injections of dexamethasone solution of 4 mg/ml for 5 consecutive days. These results were clinically significant. No complications were reported.	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 in 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.

Table 2. Cochrane Reviews on tinnitus-vestibular dysfunction (symptomatic therapy)

First author: title, year of study (year of publication)	Objectives	Selection criteria	Main results	Conclusions
Phillips: Tinnitus retraining therapy (TRT) for tinnitus, 2010 (2010)	To assess the efficacy of TRT in the treatment of tinnitus.	RCTs of TRT vs. no treatment, or other forms of treatment, in adult patients with tinnitus.	Only 1 trial (123 participants) was included in the review. Several excluded trials did not follow the strict protocol for TRT, evaluating instead a modified form of TRT. The included trial showed TRT to be more effective than a TM approach. In this study, outcome data for tinnitus severity were presented using 3 instruments (THI, THQ, and TSI) for patients in 3 groups (participants' tinnitus being a 'moderate problem', 'big problem', or 'very big problem'). At 18 months, improvements for the 3 groups in the 3 scores (TRT vs. TM) were, respectively: 'moderate problem' – THI: 18.2 vs. 4.6, THQ: 489 vs. 178, TSI: 7.5 vs. 1.6; 'big problem' – THI: 29.2 vs. 16.7, THQ: 799 vs. 256, TSI: 12.1 vs. 6.7; 'very big problem' – THI: 50.4 vs. 10.3, THQ; 1,118 vs. 300, TSI: 19.7 vs. 4.8.	A single, low-quality RCT suggests that TRT is much more effective as a treatment for patients with tinnitus than TM.
Hoekstra: Anticonvulsants for tinnitus, 2011 (2011)	To assess the effectiveness of anticonvulsants in patients with chronic tinnitus.	We selected RCTs in patients with chronic tinnitus comparing orally administered anticonvulsants with placebo. The primary outcome was improvement in tinnitus measured with validated questionnaires. Secondary outcomes were improvement in tinnitus measured with self-assessment scores, improvement in global well-being or accompanying symptoms, and adverse drug effects.	Seven trials (453 patients) were included in this review. These studies investigated 4 different anticonvulsants: gabapentin, carbamazepine, lamotrigine, and flunarizine. The risk of bias of most studies was 'high' or 'unclear'. Three studies included a validated questionnaire (primary outcome). None of them showed a significant positive effect of anticonvulsants. One study showed a significant negative effect of gabapentin compared to placebo with an increase in Tinnitus Questionnaire score of 18.4 points (SMD 0.82, 95% CI 0.07–1.58). A second study showed a positive, nonsignificant effect of gabapentin with a difference compared to placebo of 2.4 points on the THI (SMD –0.11, 95% CI –0.48 to 0.25). When the data from these 2 studies are pooled, no effect of gabapentin is found (SMD 0.07, 95% CI –0.26 to 0.40). A third study reported no differences on the THI after treatment with gabapentin compared to placebo (exact numbers could not be extracted from the article). A meta-analysis of 'any positive effect' (yes vs. no) based on a self-assessment score (secondary outcome) showed a small favorable effect of anticonvulsants (risk difference 14%, 95% CI 6–22). A meta-analysis of 'near or total eradication of tinnitus annoyance' showed no effect of anticonvulsants (risk difference 4%, 95% CI –2 to 11). Side effects of the anticonvulsants used were experienced by 18% of patients.	Current evidence regarding the effectiveness of anticonvulsants in patients with tinnitus has significant risk of bias. There is no evidence from studies performed so far to show that anticonvulsants have a large positive effect in the treatment of tinnitus, but a small effect (of doubtful clinical significance) has been demonstrated.
Hobson: Sound therapy (masking) in the management of tinnitus in adults, 2010 (2010)	To assess the effectiveness of sound-creating devices (including hearing aids) in the management of tinnitus in adults. Primary outcome measures were changes in the loudness or severity of tinnitus and/or impact on quality of life. Secondary outcome measures were change in pure-tone auditory thresholds and adverse effects of treatment.	Prospective RCTs recruiting adults with persistent, distressing, subjective tinnitus of any etiology in which the management strategy included maskers, noise-generating devices, and/or hearing aids, used either as the sole management tool or in combination with other strategies, including counseling.	Six trials (553 participants) are included in this review. Studies were varied in design, with significant heterogeneity in the evaluation of subjective tinnitus perception, with different scores, scales, tests, and questionnaires as well as variance in the outcome measures used to assess the improvement in tinnitus sensation/quality of life. This precluded a meta-analysis of the data. There was no long-term follow-up. We assessed the risk of bias as medium in 3 and high in 3 studies. Following analysis of the data, no significant change was seen in the loudness of tinnitus or the overall severity of tinnitus after the use of sound therapy compared to other interventions such as patient education, 'relaxation techniques', 'tinnitus coping strategies', counseling, 'tinnitus retraining', and exposure to environmental sounds. No side effects or significant morbidity were reported from the use of sound-creating devices.	The limited data from the included studies failed to show strong evidence of the efficacy of sound therapy in tinnitus management. The absence of conclusive evidence should not be interpreted as evidence of lack of effectiveness. The lack of quality research in this area, in addition to the common use of combined approaches (hearing therapy plus counseling) in the management of tinnitus are, in part, responsible for the lack of conclusive evidence. Other combined forms of management, such as tinnitus retraining therapy, have been subject to a Cochrane Review. Optimal management may involve multiple strategies.
Hilton: Ginkgo biloba for tinnitus, 2004 (2013)	To assess the effect of ginkgo biloba in patients who are troubled by tinnitus.	Adults (18 years and over) complaining of tinnitus or adults with a primary complaint of cerebral insufficiency, where tinnitus forms part of the syndrome.	Four trials with a total of 1,543 participants were included in the review; we assessed all the included studies as having a low risk of bias. Three trials (1,143 participants) included patients with a primary complaint of tinnitus, and 1 (400 participants) included patients with mild to moderate dementia, some of whom had tinnitus. There was no evidence that ginkgo biloba was effective in patients with a primary complaint of tinnitus. In the study of patients with dementia, mean baseline levels of tinnitus were low (1.7–2.5 on a 10-point subjective symptom rating scale). A small but statistically significant reduction of 1.5 and 0.7 points was seen in patients taking ginkgo biloba with vascular dementia and Alzheimer's disease, respectively. The practical clinical significance of this is unclear. The incidence of side effects was low.	The limited evidence does not demonstrate that ginkgo biloba is effective for tinnitus when this is the primary complaint.

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Table 2. (continued)

First author: title, year of study (year of publication)	Objectives	Selection criteria	Main results	Conclusions
Martinez-Devesa: Cognitive behavioural therapy for tinnitus, 2007 (2010)	To assess whether CBT is effective in the management of patients suffering from tinnitus.	RCTs in which patients with unilateral or bilateral tinnitus as their main symptom received CBT.	Eight trials comprising 468 participants were included. For the primary outcome of subjective tinnitus loudness, we found no evidence of a difference between CBT and no treatment or another intervention (yoga, education, and 'minimal contact education'). In the secondary outcomes, we found evidence that quality of life scores were improved in participants who had tinnitus when comparing CBT to no treatment or another intervention (education and 'minimal contact education'). We also found evidence that depression scores improved when comparing CBT to no treatment. We found no evidence of benefit in depression scores when comparing CBT to other treatments (yoga, education, and 'minimal contact education'). There were no adverse/side effects reported in any trial.	In 6 studies, we found no evidence of a significant difference in the subjective loudness of tinnitus. However, we found a significant improvement in depression score (in 6 studies) and quality of life (decrease of global tinnitus severity) in another 5 studies, suggesting that CBT has a positive effect on the management of tinnitus.
Meng: Repetitive transcranial magnetic stimulation for tinnitus, 2011 (2011)	To assess the effectiveness and safety of rTMS vs. placebo in patients with tinnitus.	RCTs of rTMS vs. sham rTMS.	Five trials including 233 participants met our inclusion criteria. Each study described the use of a different rTMS device that delivered different waveforms at different frequencies. All 5 trials were relatively small studies, but generally, they demonstrated a low risk of bias. When considering the impact of tinnitus on patients' quality of life, the results of only 1 study demonstrated a statistically significant improvement in THI scores at 4 month follow-up (defined as a 'partial improvement' by the study authors; THI reduction of 21–80%) when low-frequency rTMS was compared with a sham control treatment. However, no statistically significant improvement was demonstrated by another 2 studies that considered rTMS at the same frequency. Furthermore, this single positive finding should be taken in the context of the many different variables which were recorded at many different points in time by the study authors. In accordance with our prespecified subgroup analysis, we extracted the data from 1 study to consider the differential effectiveness between 'lower' low-frequency rTMS (1 Hz) and 'higher' low-frequency rTMS (10 and 25 Hz). In doing this, we were able to demonstrate a statistically significant difference between rTMS employing a frequency of 1 Hz and the sham group when considering tinnitus severity and disability after 4 months of follow-up ('partial' improvement). However, no statistically significant difference was demonstrated between 10- and 25-Hz rTMS and the sham control group, when considering the severity and disability of tinnitus at the 4-month follow-up. When considering tinnitus loudness in patients undergoing rTMS, we were able to demonstrate a statistically significant reduction in tinnitus loudness when the results of 2 studies were pooled (risk ratio 4.17, 95% CI 1.30–13.40). However, this finding was based on 2 small trials and, consequently, the CI was particularly wide. No serious adverse effects were reported in any of the trials.	There is very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus. When considering the impact of tinnitus on patients' quality of life, support is from a single study with a low risk of bias based on a single outcome measure at a single point in time. When considering the impact on tinnitus loudness, this is based on the analysis of pooled data with a large CI. Studies suggest that rTMS is a safe treatment for tinnitus in the short term; however, there were insufficient data to provide any support for the safety of this treatment in the long term. More prospective randomized placebo-controlled double-blind studies with large sample sizes are needed to confirm the effectiveness of rTMS for tinnitus patients. Uniform validated tinnitus-specific questionnaires and measurement scales should be used in future studies.
Baldo: Antidepressants for patients with tinnitus, 2006 (2012)	To assess the effectiveness of antidepressants in the treatment of tinnitus and to ascertain whether any benefit is due to a direct tinnitus effect or a secondary effect due to treatment of concomitant depressive states.	Randomized controlled clinical studies of antidepressant drugs vs. placebo in patients with tinnitus.	Six trials involving 610 patients were included. Trial quality was generally low. Four of the trials looked at the effect of tricyclic antidepressants on tinnitus, investigating 405 patients. One trial investigated the effect of an SSRI in a group of 120 patients. One study investigated trazodone, an atypical antidepressant, vs. placebo. Only the trial using the SSRI drug reached the highest quality standard. None of the other included trials met the highest quality standard, due to use of inadequate outcome measures, large drop-out rates, or failure to separate the effects on tinnitus from the effects on symptoms of anxiety and depression. All the trials assessing tricyclic antidepressants suggested that there was a slight improvement in tinnitus, but these effects may have been attributable to methodological bias. The trial that investigated the SSRI drug found no overall improvement in any of the validated outcome measures that were used in the study, although there was possible benefit for a subgroup that received higher doses of the drug. This observation merits further investigation. In the trial investigating trazodone, the results showed an improvement in tinnitus intensity and in quality of life after treatment, but in neither case reached statistical significance. Reports of side effects including sedation, sexual dysfunction, and dry mouth were common.	There is as yet insufficient evidence to say that antidepressant drug therapy improves tinnitus.

Table 2. (continued)

First author: title, year of study (year of publication)	Objectives	Selection criteria	Main results	Conclusions
Bennett: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus, 2005 (2012)	To assess the benefits and harms of HBOT for treating ISSHL and/or tinnitus.	Randomized studies comparing the effect on ISSHL and tinnitus of HBOT and alternative therapies.	Seven trials contributed to this review (392 participants). The studies were small and of generally poor quality. Pooled data from 2 trials did not show any significant improvement in the chance of a 50% increase in hearing threshold on pure-tone average with HBOT (RR with HBOT 1.53, 95% CI 0.85–2.78, p = 0.16), but did show a significantly increased chance of a 25% increase in pure-tone average (RR 1.39, 95% CI 1.05–1.84, p = 0.02). There was a 22% greater chance of improvement with HBOT, and the number needed to treat to achieve one extra good outcome was 5 (95% CI 3–20). There was also an absolute improvement in average pure-tone audiometric threshold following HBOT (mean difference 15.6 dB greater with HBOT, 95% CI 1.5–29.8, p = 0.03). The significance of any improvement in tinnitus could not be assessed. There were no significant improvements in hearing or tinnitus reported for chronic presentation (6 months) of ISSHL and/or tinnitus.	For people with acute ISSHL, the application of HBOT significantly improved hearing, but the clinical significance remains unclear. We could not assess the effect of HBOT on tinnitus by pooled analysis. In view of the modest number of patients, methodological shortcomings, and poor reporting, this result should be interpreted cautiously. An appropriately powered trial is justified to define those patients (if any) who can be expected to derive most benefit from HBOT. There is no evidence of a beneficial effect of HBOT on chronic ISSHL or tinnitus and we do not recommend the use of HBOT for this purpose.
Hoare: Amplification with hearing aids for patients with tinnitus and co-existing hearing loss, 2014 (2014)	To assess the effects of hearing aids specifically in terms of tinnitus benefit in patients with tinnitus and coexisting hearing loss.	RCTs and non-RCTs recruiting adults with subjective tinnitus and some degree of hearing loss, where the intervention involves amplification with hearing aids and this is compared to interventions involving other medical devices, other forms of standard or complementary therapy, or combinations of therapies, no intervention or placebo interventions.	One RCT (91 participants) was included in this review. We judged the trial to have a low risk of bias for method of randomization and outcome reporting and an unclear risk of bias for other criteria. No non-RCTs meeting our inclusion criteria were identified. The included study measured change in tinnitus severity (primary measure of interest) using a tinnitus questionnaire measure, and change in tinnitus loudness (secondary measure of interest) on a visual analogue scale. Other secondary outcome measures of interest, namely change in the psychoacoustic characteristics of tinnitus, change in self-reported anxiety, depression and quality of life, and change in neurophysiological measures, were not investigated in this study. The included study compared hearing aid use to sound generator use. The estimated effect on change in tinnitus loudness or severity as measured by the THI score was compatible with benefits for both hearing aids or sound generators, but no difference was found between the two alternative treatments (mean difference −0.90, 95% CI −7.92 to 6.12; 100-point scale); moderate-quality evidence. No negative or adverse events were reported.	The current evidence base for hearing aid prescription for tinnitus is limited. To be useful, future studies should make appropriate use of blinding and be consistent in their use of outcome measures. Whilst hearing aids are sometimes prescribed as part of tinnitus management, there is currently no evidence to support or refute their use as a more routine intervention for tinnitus.
Hiller: Vestibular rehabilitation for unilateral peripheral vestibular dysfunction, 2007 (2011)	To assess the effectiveness of VR in the adult community-dwelling population of people with symptomatic unilateral peripheral vestibular dysfunction.	Randomized trials of adults living in the community, diagnosed with symptomatic unilateral peripheral vestibular dysfunction. We sought comparisons of VR vs. control (placebo etc.), other treatment (non-VR, e.g. pharmacological), or another form of VR. We considered the outcome measures of frequency and severity of dizziness or visual disturbance; changes in balance impairment, function, or quality of life; and measure/s of physiological status with known functional correlation.	We included 27 trials, involving 1,668 participants, in the review. Trials addressed the effectiveness of VR against control/sham interventions, medical interventions, or other forms of VR. Individual and pooled data showed a statistically significant effect in favor of VR over control or no intervention. The exception to this was when movement-based VR was compared to physical maneuvers for BPPV, where the latter was shown to be superior in cure rate in the short term. There were no reported adverse effects.	There is moderate to strong evidence that VR is a safe, effective management for unilateral peripheral vestibular dysfunction, based on a number of high-quality RCTs. There is moderate evidence that VR provides a resolution of symptoms and improvement in functioning in the medium term. However, there is evidence that for the specific diagnostic group of BPPV, physical (repositioning) maneuvers are more effective in the short term than exercise-based VR, although a combination of the two is effective for longer-term functional recovery. There is insufficient evidence to discriminate between differing forms of VR.

TRT = Tinnitus retraining therapy; TM = tinnitus masking; THI = Tinnitus Handicap Inventory; THQ = Tinnitus Handicap Questionnaire; TSI = Tinnitus Severity Index; SMD = standardized mean difference; CI = confidence interval; SSRI = selective serotonin reuptake inhibitor; HBOT = hyperbaric oxygen therapy; ISSHL = idiopathic sudden sensorineural hearing loss; RR = risk ratio; VR = vestibular rehabilitation; BPPV = benign paroxysmal positional vertigo.

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and Burton, 2001]. Despite the 243 patients included in the systematic review, which may correspond roughly to the affected population of a big European city or a little region with less than 1 million inhabitants, the authors concluded that the evidence for any effect was insufficient. Moreover, despite the efforts over the years to improve the reporting of adverse effects [Loke et al., 2007], systematic reviews still tend to underreport them [Zorzela et al., 2014]; so, not only insufficient evidence exists for positive effects of the treatment with betahistine, but also its harmful effects may be underestimated. In fact, different studies have shown that betahistine can cause bronchospasms [Jeck-Thole and Wagner, 2006; White et al., 1987] and, according to Food and Drug Administration, betahistine dihydrochloride 'has caused asthma, drowsiness, lethargy, nausea, headache. Could cause eye and skin irritation, and inhalation should be prevented. Could cause recurrence of peptic ulcers due to its histamine-like activity' (http://www.fda.gov/ohrms/dockets/ac/98/briefingbook/1998-3454b1_02_15-bdl02.pdf). These aspects should be taken into account in a comprehensive patient-centered evaluation which considers not only the positive effects and the efficacy of an intervention in 'ideal' trial conditions, but also the effectiveness [Witt, 2009] in a usual or routine care condition together with side effects. Moreover, establishing the efficacy of any intervention for a rare disease, such as Ménière's disease, may be difficult because of the limited number of patients [Behera et al., 2007]. Moreover, many patients may not be eligible for the trials, for example, because of concurrent conditions or previous and current treatments listed in the exclusion criteria of the trials. Therefore, evidence-based methodology in rare diseases can help minimize bias and maximize the truth of observed new data; however, RCTs in case of rare diseases may often not be feasible or available. Therefore, more attention should be paid to all the available sources of evidence (not only RCTs). A circular instead of a hierarchical method can be particularly informative in case of a rare disease [Olsen et al., 2011] because it considers not only RCTs, but also outcomes and cohort studies as sources of evidence [Walach et al., 2006]. Even considering all of these aspects, or the fact that trials with lower-quality standards have shown some slight reduction of vertigo or tinnitus that may have benefitted some patients, from a patient-centered perspective, betahistine cannot be considered as a gold standard therapy for Ménière's disease, and it seems not to be effective for the majority of the treated population. Similar conclusions can be drawn for diuretics, also prescribed by 63% of the surgeons in the UK for Ménière's disease [Smith et al., 2005] despite the lack of evidence of their effectiveness and the important burden of evidence of their side effects, particularly during long-term treatment [Pirmohamed et al., 2004; Pirodda et al., 2011]. Endolymphatic sac surgery also seems not to have any significant effects in the majority of the treated population with Ménière's disease, although new techniques have shown some positive results [Goto et al., 2012], but again, its side effects may be underestimated [Xu et al., 2011]. Intratympanic steroids, despite the small population included in the trial (only 22 individuals), have been shown to be an effective treatment, with improvement of the frequency and severity of vertigo lasting for over 2 years [Phillips and Westerberg, 2011]. A retrospective study (on 22 individuals) [Dodson et al., 2004] has shown only short-term positive effects (in half of the treated population) and no long-term effects, but another recent retrospective study (on 20 individuals) [Chen et al., 2011] has confirmed that positive effects of the treatment on vertigo lasted over 12 months. Intratympanic gentamicin has been proved to be an effective treatment for vestibular symptoms of Ménière's disease [Pullens and van Benthem, 2011]. However, dose-dependent adverse effects [Casani et al., 2014] are experienced by a large proportion of the treated population (up to 25% of the treated population experienced hearing loss in the trials included in the Cochrane Review). These adverse effects, together with its noneffectiveness for the other two main symptoms of the typical clinical triad of Ménière's disease syndrome, tinnitus and hearing loss (often worsened by this therapy), are major drawbacks for an etiological therapy, proving once more that 'there is no single treatment for Ménière's disease'.

Notably, symptomatic therapies of tinnitus and vestibular dysfunctions that have been proven to be effective, or at least significantly improved quality of life or depression, are all nonpharmacological treatments: tinnitus retraining therapy, sound therapy (masking), CBT, and vestibular rehabilitation [Hillier and McDonnell, 2011; Hobson et al., 2010; Martinez-Devesa et al., 2010; Phillips and McFerran, 2010]. Even more interesting is the fact that these treatments seem to be particularly safe. Therefore, the suggestion by Hobson et al. [2010] in their review on sound therapy (masking) that 'optimal management may involve multiple strategies' seems to be a safe and practically available option involving nonpharmacological symptomatic treatments. Also hearing aids in patients with tinnitus and coexisting hearing loss seem very safe, although there is still limited evidence of their

effectiveness [Hoare et al., 2014]. On the other hand, not only anticonvulsants and antidepressants were not effective, but their adverse effects are important: as reported by the Cochrane Reviews, 'side effects of the anticonvulsants used were experienced by 18% of patients' [Hoekstra et al., 2011], and for antidepressants, 'reports of side effects including sedation, sexual dysfunction and dry mouth were common' [Baldo et al., 2012]. Most of the serious side effects of these drugs are already listed in the drug labels or reported in the literature, including hearing loss [de la Cruz and Bance, 1999] and higher suicidal risk [Gunnell et al., 2005]. Although a small but statistically significant reduction of tinnitus was seen in patients taking ginkgo biloba with vascular dementia and Alzheimer's disease, there was no evidence that ginkgo biloba was effective in patients with a primary complaint of tinnitus [Hilton et al., 2013]. Ginkgo biloba has recently been proven to be an experimental carcinogen in bioassays on both mice and rats [Dunnick and Nyska, 2013]; therefore, the physician should carefully consider its side effects before using it, especially for long-term treatments.

Considering the lack of gold standard etiologic and symptomatic treatments for Ménière's disease, we checked the literature for other possible therapy options, starting with studies for which a risk of bias had already been assessed in other Cochrane Reviews, as in the case of tai chi: two studies, already included in the Cochrane Reviews in order to study the effectiveness of vestibular rehabilitation for unilateral peripheral vestibular dysfunction [Hillier and McDonnell, 2011], have also concurrently demonstrated the effectiveness of tai chi for vestibular dysfunctions [McGibbon et al., 2004, 2005]. Other articles have elucidated the effectiveness of tai chi for vestibulopathy, which also appears useful and extremely safe for a variety of nonvestibulopathy etiologic balance disorders [Lee, 2009; Lee et al., 2012; MacIaszek and Osinski, 2012; Wayne et al., 2004].

More controversial and a matter of debate for over 40 years is the effectiveness of acupuncture for the treatment of tinnitus: the different techniques and materials used, together with a strong operator dependency of acupuncture itself, may at least in part explain the strong heterogeneity of the results observed by different authors [Andersson and Lyttkens, 1996; Axelsson et al., 1994; Hansen et al., 1982; Mann, 1974; Marks et al., 1984; Meehan et al., 2004]. Wang et al. [2010], in a randomized placebo-controlled trial involving 50 patients with manual and electrical acupuncture for the treatment of tinnitus, observed no statistically significant difference at any stage for tinnitus occurrence ($p > 0.111$) and loudness ($p > 0.079$) in the patients treated with manual and electrical acupuncture compared to the placebo groups. Two recent systematic reviews on acupuncture and tinnitus could not reach definitive conclusions on the effectiveness of this treatment: 'the number, size and quality of the RCTs on the effectiveness of acupuncture for the treatment of tinnitus are not sufficient for drawing definitive conclusions' [Kim et al., 2012] and 'acupuncture points and sessions used in Chinese studies may be more appropriate, whereas these studies have many methodological flaws and risk bias, which prevents us making a definitive conclusion' [Liu et al., 2014]. A systematic review by the Cochrane Collaboration on acupuncture for tinnitus [Li et al., 2009] is currently in progress.

Zinc treatment was also recently investigated for the treatment of tinnitus. Treatment with systemic zinc has been able to change some aspects of auditory neurotransmission in the brain stem; in particular, it induced significant prolongation of the wave V latency and an enlargement of the wave V amplitude [Person et al., 2010]. A recent randomized placebo-controlled crossover trial in an elderly population showed an improvement of tinnitus, although not statistically significant, in the treated population compared to placebo: 5% (5 of 93 patients) had an improvement of 20 points or greater in the Tinnitus Handicap Questionnaire scores after zinc treatment, whereas 2% (2 of 94 patients) had an improvement of 20 or greater in Tinnitus Handicap Questionnaire scores after placebo [Coelho et al., 2013]. A systematic review by the Cochrane Collaboration on zinc supplementation for tinnitus is currently in progress [Person et al., 2012].

Abnormal cochlear microcirculation has recently been identified as an important etiologic factor in Ménière's disease [Olivetto et al., 2012], and it is already well documented as a causal factor in noise-induced hearing loss, age-related hearing loss (presbycusis), sudden hearing loss, or vestibular function [Shi, 2011]. To our knowledge, Godlowski was the first to point out the importance of microcirculation in the etiopathogenesis of Ménière's syndrome already in 1965. Understanding the mechanisms underlying the pathophysiology of cochlear microcirculation is of fundamental clinical importance for Ménière's disease. The etiopathogenic role of vasopressin imbalance in the stria vascularis affecting microcirculation was recently elucidated in experimental animal models [Egami et al., 2013; Kakigi, 2013], becoming a promising target of new etiologic therapies [Naganuma, 2013]. Obstruction of the distal part of the

vein of the vestibular aqueduct in experimental animals causes disturbances in the endolymph homeostasis and potentially symptoms similar to the ones of Ménière's disease [Friis and Qvortrup, 2007], confirming previous observations in humans affected by Ménière's disease who presented with occlusion of the vein of the vestibular aqueduct. Central nervous system vein occlusions seem to play a role in the syndrome; in fact, chronic cerebrospinal vein insufficiency is also significantly increased in Ménière's disease patients [Alpini et al., 2013; Filipo et al., 2015] compared to controls, and preliminary results have shown significant improvement of the symptoms in patients with Ménière's disease and chronic cerebrospinal vein insufficiency treated with percutaneous transluminal angioplasty [Bruno et al., 2013]. Patients with concurrent multiple sclerosis and Ménière's disease, who are treated with percutaneous transluminal angioplasty for multiple sclerosis, may be considered as a potential elite cohort for further studies and analysis.

Currently, Ménière's disease is recognized as a rare disease by the scientific community and is listed as a rare disease by Orphanet (the portal of rare diseases and drugs supervised by the European Commission, Orpha, ORPHA45360, http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=45360), by the Office of Rare Diseases Research of the National Institute of Health (http://rarediseases.info.nih.gov/gard/10340/menieres-disease/more-about-this-disease), and by the National Organization for Rare Disorders (http://www.rarediseases.org/rare-disease-information/rare-diseases/byID/272/viewFullReport). Despite the wide scientific consensus, Ménière's disease is not as widely legally recognized as a potentially disabling condition, for example, it is recognized as such by the US Social Security Administration, but not yet by the Italian law (http://www.senato.it/japp/bgt/showdoc/frame.jsp?tipodoc=SommComm&leg=17&id=00716920&part=doc_dc&parse=no). This is a great matter of concern, particularly in light of the impaired ability to work and the several limitations which Ménière's disease patients already suffer from: in a recent evaluation of quality of life through the World Health Organization's International Classification of Functioning, Disability and Health, 70% reported impairments, 39% activity limitations, 47% participation restrictions, 16% effects on environmental contextual factors, and 28% effects on personal contextual factors [Levo et al., 2010].

Therefore, it is important to underline, particularly from a patient-centered perspective, that a lack of recognition by local institutions of Ménière's disease and limited access to appropriate treatments may undermine the quality of care for these patients. In fact, sometimes, this disease is still misdiagnosed as a psychosomatic disorder [Fowler and Zeckel, 1952; Martin et al., 1991], despite the overwhelming evidence for its organic origin [Clemmens and Ruckenstein, 2012; Pyykko et al., 2013].

Conclusions

There is currently no gold standard etiological treatment for Ménière's disease. Evidence from Cochrane Reviews shows that Ménière's disease patients may benefit from intratympanic gentamicin or steroid etiologic therapies [Phillips and Westerberg, 2011; Pullens and van Benthem, 2011], but these may induce serious side effects: for example, intratympanic gentamicin is effective for treating vestibular complaints but is not effective for treating tinnitus and hearing loss, which is often worsened by the therapy in up to 25% of the treated population. All the etiologic and symptomatic treatments based on oral drug regimens evaluated in the Cochrane Reviews did not prove their effectiveness and may induce important adverse effects [Baldo et al., 2012; Burgess and Kundu, 2006; Hoekstra et al., 2011; James and Burton, 2001]. Interestingly, the evidence from Cochrane Reviews highlights several effective symptomatic treatments for tinnitus and vestibular complaints that are nonpharmacological: tinnitus retraining therapy, sound therapy (masking), CBT, and vestibular rehabilitation [Hillier and McDonnell, 2011; Hobson et al., 2010; Martinez-Devesa et al., 2010; Phillips and McFerran, 2010]. The positive safety profiles of these treatments allow multiple therapy strategies with limited risks of serious side effects. Tai chi seems to be another promising and safe option for treating vestibular symptoms in Ménière's disease [McGibbon et al., 2004, 2005]. Following the recent discoveries on the microvascular etiopathogenesis of Ménière's disease, more trials are needed to confirm the first positive results obtained by etiological treatments aimed to improve the microcirculation of the inner ear [Bruno et al., 2013; Naganuma, 2013].

Finally, the active involvement of a patient representative in this review helped all the authors to focus on some fundamental patient needs: balancing the evaluations of treatment efficacy and side effects through circular, rather than hierarchical, approaches to gain evidence for an optimal patient-centered care [Olsen et al., 2011] and improving the legal recognition of Ménière's disease as a

rare disease caused by endolymphatic hydrops because still too many cases are misdiagnosed as psychosomatic disorders [Martin et al., 1991].

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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