Menière's disease

CLINICAL ASPECTS DIAGNOSTIC TESTS AND INTERVENTIONS

Babette van Esch

MENIÈRE'S DISEASE: CLINICAL ASPECTS, DIAGNOSTIC TESTS AND INTERVENTIONS

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MENIÈRE'S DISEASE: CLINICAL ASPECTS, DIAGNOSTIC TESTS AND INTERVENTIONS

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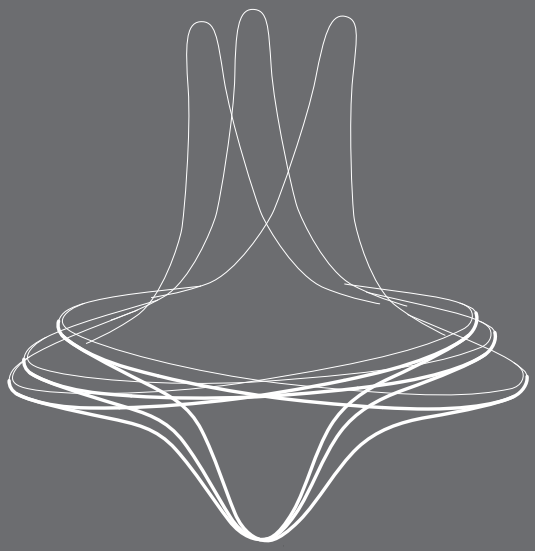
Voor mijn ouders en mijn broer



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GENERAL INTRODUCTION, THESIS OUTLINE AND RESEARCH QUESTIONS

Historical perspective

In 1861, Prosper Menière (1779-1862) published five papers that are now widely known as the primary reference for the concept of 'Menière's Disease' (MD) [1]. In these papers in the 'Gazette Médicinale de Paris', he described patients who suffered from a triad of symptoms: recurring spontaneous attacks of vertigo accompanied by hearing loss and tinnitus. He described that the attacks of vertigo were often accompanied by symptoms of nausea and vomiting and that the loss of hearing and tinnitus increased in severity over time [2].
Prior to the pioneering work of Menière, it was generally accepted that the central nervous system was entirely responsible for symptoms of vertigo [3]. Vertigo was lumped together with other central nervous disorders known as the 'symptomatology of apoplectiform cerebral congestion'. At that time, it was believed that the inner ear was composed of several parts that were all involved in mediating different aspects of sound [4]. Although the establishment of a relationship between the vestibular apparatus and the maintenance of head positions and balance was already accomplished by Flourens in 1824 [5], it was not applied in human science until Menière's remarks were published.

Definition of MD

Over time, there have been many different definitions of MD. All methods to define MD have been symptom-based [6]. The diagnostic criteria describe the type and character of vertigo, the amount of associated hearing loss, the presence of tinnitus and/or aural fullness and in all cases other causes are excluded. In 1972, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) first defined MD as an inner ear disease of the membranous part of the labyrinth with characteristic symptoms and a correlation with endolymphatic hydrops [7] (see section Pathophysiology). The criteria have been updated three times, in 1985, in 1995 and in 2015 [8,9, 10]. The latest set of diagnostic criteria was jointly formulated by the Classification Committee of the Bárány Society, the Japan Society of Equilibrium Research, the European Academy of Otology and Neurotology, the AAO-HNS and the Korean Balance Society to facilitate future collaborative studies [10]. However, as these international diagnostic criteria were only published recently and previous research widely used the AAO-HNS 1995 diagnostic guidelines, the latter set of criteria will be used in the current thesis. The AAO-HNS 1995 diagnostic criteria are shown in **Table 1**.

TABLE 1. The American Academy of Otolaryngology –Head and Neck Surgery criteria as published in 1995 [9].

Certain MD	Definite MD	Histopathological confirmation	
Definite MD	Two or more definitive spontaneous episodes of vertigo 20 minutes or longer	Audiometrically documented hearing loss on at least one occasion	Tinnitus or aural fullness in the treated ear
Probable MD	One definitive episode of vertigo	Audiometrically documented hearing loss on at least one occasion	Tinnitus or aural fullness in the treated ear
Possible MD	Episodic vertigo of the Menière type without documented hearing loss	Sensorineural hearing loss, fluctuated or fixed, with disequilibrium but without definitive episodes	

Pathophysiology

As mentioned in the *Historical perspective section*, the papers published by Prosper Menière were the first to describe a relationship between the maintenance of balance and the inner ear. The inner ear structures that convey information about balance are found in the petrous part of the temporal bone (see **Figure 1**) [11].

The bony labyrinth is located inside the temporal bone. It consists of a series of cavities: the three semicircular canals, the vestibule and the cochlea. The bony structures protect the membranous part of the labyrinth which is divided into a perilymphatic and an endolymphatic compartment. The membranous labyrinth consists of three semicircular ducts, two otolith organs, the utricle and saccule, and the cochlear duct. The semicircular ducts and the otolith organs convey information on balance whereas the cochlear duct is the organ of hearing.

Although the pathogenesis of MD is currently still unknown, it is generally accepted that the origin of the disease lies within the endolymphatic system of the membranous labyrinth. In 1938, two independent researchers performed autopsy on human temporal bone which revealed hydrops of the endolymphatic system [13,14]. Idiopathic endolymphatic hydrops is thought to be caused by either an over-production or an under-absorption of endolymph. The classical theory hypothesises that endolymphatic hydrops eventually causes Reissner's membrane to rupture (Menière crisis) [14]. Subsequently, potassium-rich endolymph escapes

into the sodium- rich perilymph leading to neurotoxic effects on the hair cells, causing loss of hearing and vestibular function.

Idiopathic endolymphatic hydrops is believed to be the etiological substrate of MD. A recent review reported that it is almost certain that in patients with unilateral 'definite' MD, at least one temporal bone shows endolymphatic hydrops [15]. Moreover, hydrops was also found in asymptomatic contralateral ears in patients with unilateral MD [16,17]. Therefore, endolymphatic hydrops may be regarded as a necessary histopathological finding, at least in definite unilateral MD.

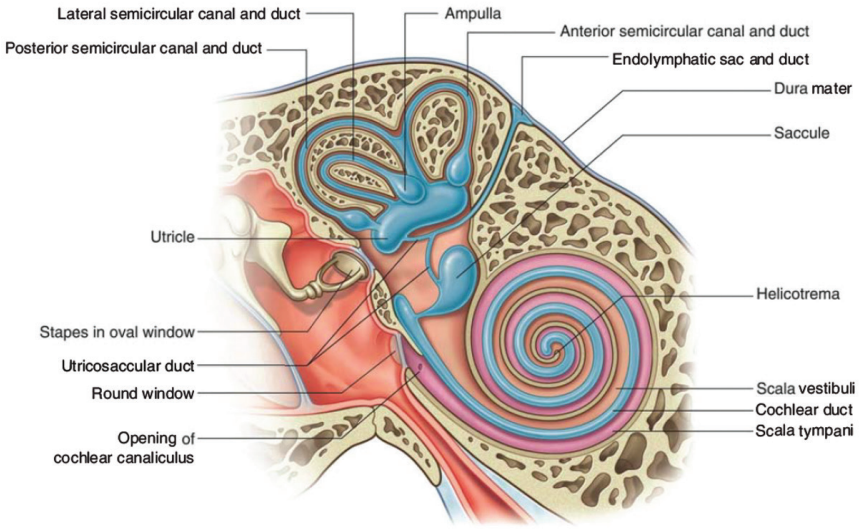

Figure 1. The labyrinth – Gray's anatomy for students [12].

Prevalence of MD

Although the cardinal symptoms of MD are spontaneous attacks of vertigo spells, hearing loss and tinnitus, in the presence of aural fullness, there is a great variety in the presenting symptoms. Symptoms do not necessarily manifest themselves simultaneously and there may be a delay of several years between the first symptoms and the definitive diagnosis [18,19]. When reviewing the literature on the prevalence of MD, rates from 3.5 per 100.000 to 513 per 100.000 inhabitants have been reported [20-22]. The wide range of values is most likely to be due to the inconsistency in defining and redefining the diagnosis over time, differences in study methods, (retrospective and prospective designs) and difficulty in distinguishing MD from related conditions (e.g. vestibular migraine (VM)). In general, these factors complicate the summation of epidemiological aspects of MD [23-25]. Based on research in the Netherlands, the prevalence has been estimated at 0.6 to 1.0 per 1000 inhabitants, cumulating in 15.000 MD patients [19,26].

Age of onset of disease

In reviewing the literature regarding the age of onset, it is safe to say that MD generally develops in middle age [27]. The peak incidence in onset of the disease lies in the fourth and fifth decade of life [28], but even onset later in life, during the sixth and seventh decade, is not an uncommon finding [29].

Recently, a Japanese survey reported a progressive increase in the age of onset of MD which was explained by the increase of the working elderly population. It was proposed that work-related stress might contribute to the development of MD [30,31]. In **Chapter 2** we will evaluate the age of onset of MD patients who visited a tertiary dizziness centre in the Netherlands. In addition, it will investigate whether a shift towards a later age of onset is also present in the Dutch MD population similar to the Japanese population.

Clinical course of MD

Understanding the natural history of MD is of paramount value to develop treatment strategies and time the follow-up moments of the efficacy and effectiveness of treatment modalities. However, the incapacitating character of the disease makes it difficult to abstain from treatment and patients tend to consult more than one physician which often results in different forms of treatment [32]. Any treatment, such as lifestyle changes or dietary modifications, may alter the natural course of the disease, even though a beneficial effect of the specific treatment has not been established [33]. As a result, there is limited information regarding the natural course of the disease [34], which inhibits the interpretation of treatment effects in the absence of a placebo. Nonetheless, the next section will attempt to provide information on the clinical course of each symptom of MD. Results should be interpreted with caution as the course of symptoms was assessed in various MD populations, different study design and in presence of various forms of therapy.

Vertigo symptoms

Episodes of spontaneous vertigo spells may be considered as the hallmark of the disease and are often experienced as debilitating. The AAO-HNS has defined that a definitive spell of MD occurs spontaneously, causes rotational vertigo which lasts at least 20 minutes (commonly several hours) and is accompanied by disequilibrium that may persist for several days [9]. Generally, it is accompanied by nausea and vomiting. In addition, hearing loss and tinnitus tend to worsen with the onset of vertigo.

A recent large prospective study (n=510) analysed the frequency and duration of definitive spells in patients who met the diagnostic criteria for 'definite' MD [35] and who received pharmacological treatment (administration of betahistine dihydrochloride or diuretic agents) or dietary modifications. The results indicated that two phases might exist in the course of the disease. In phase 1, the initial high frequency of vertigo rapidly declines over

the first 8 years. In Phase 2, covering years 9 to 20, vertigo attacks gradually decrease. The mean frequency of vertigo spells related to the duration of disease are shown in **Figure 2**.

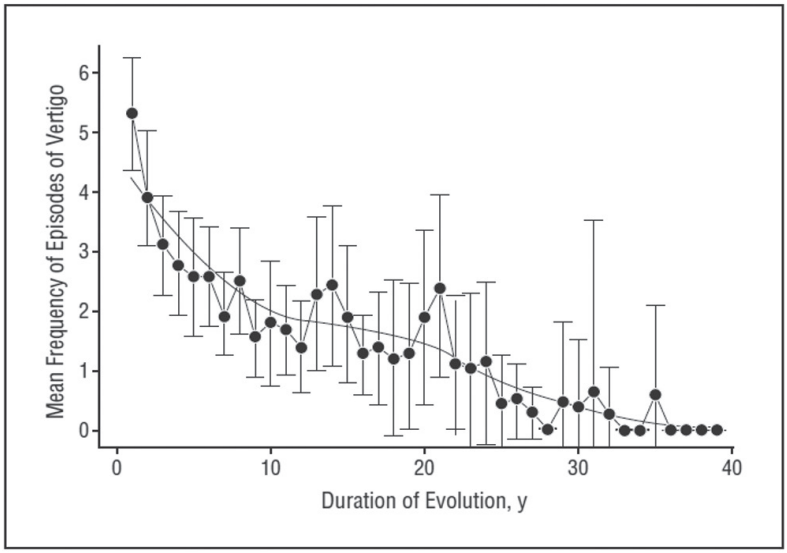

Figure 2. Mean frequency of episodes of vertigo per year of MD evolution. Bars indicate 95% intervals [34].

Previous studies demonstrated that MD can be associated with other diseases causing dizziness, such as Benign Paroxysmal Positional Vertigo (BPPV)[36-38] and psychological distress [39,40]. However, these studies [36-40] assessed the prevalence of a single comorbidity within MD populations. To date, it is still unknown which causes of dizziness most commonly coincide alongside MD. In **Chapter 3** we will quantify the prevalence of second causes of dizziness alongside MD including a reply to a letter to the editor (**Chapter 4**).

Auditory symptoms

In MD, sensorineural hearing deteriorates over the years [41-43]. It typically starts with an up-sloping low-frequency hearing loss and ends with a flat sensorineural hearing loss. Moreover, profound hearing loss (> 50 dB) is a rare finding [43]. A study in Sweden showed that 82% of the patients had a hearing loss of less than 30 dB [43]. After a follow-up of 21 years or more, the hearing further deteriorated but stabilized at a level around 50 dB which is illustrated in **Figure 3**.

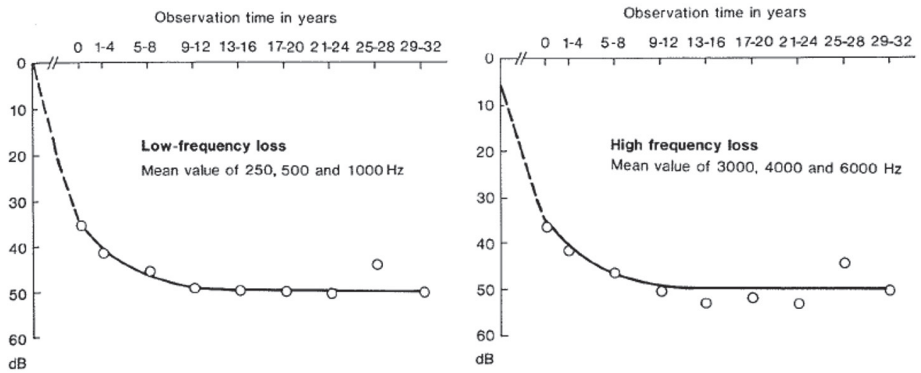

Figure 3. Hearing profile in 161 patients with Meniere's disease [43].

Tinnitus commonly involves a low-frequency type and it has been reported in up to 67% of the patients and was reported as the most incapacitating symptom in the triad of symptoms of MD [44]. A retrospective study [45] found that tinnitus increased when hearing deteriorated, and that patients with an early onset of disease and a bilateral form of MD experienced tinnitus more intensively. Aural fullness is another symptom that, similar to tinnitus, is experienced in two thirds of the MD patients [46]. In a retrospective cohort study, tinnitus, hyperacusis and balance problems were considered to be significant predictors of aural fullness [46].

Balance problems

Whilst treatment of MD is directed at reducing vertigo spells, hearing loss and tinnitus, problems with balance become more prevalent with the progression of disease [47,48]. To date, little attention has been focussed on symptoms of disequilibrium and unsteadiness in patients with MD. However, there has been increasing interest in the value of exercises for patients with balance disorders, known as vestibular rehabilitation (VR) [49].

VR includes Brandt-Daroff exercises, Cawthorne-Cooksey exercises, viewing exercises or balance exercises. By stimulating the vestibular system VR aims to improve the visual-vestibular interaction, to increase the static and the dynamic postural stability and to positively affect the quality of life by reducing complaints of imbalance, dizziness and anxiety [50]. The clinical recovery is thought to be based on three aspects. First, there is compensation/habituation, which is a central process and refers to the reduction in symptoms produced by specific movement and occurs through repetitive exposure to the movement. Secondly, there is adaptation, which is the recovery of the dynamic vestibulo-

ocular responses due to the ability of the vestibular system to make long-term changes in the neuronal response to input. Last, there is substitution, which is the use of other strategies to replace the lost function [51,52]. The effect of VR on MD will be evaluated in **Chapter 8** based on a systematic review of current literature.

Diagnostic assessment

As true today as it was in Prosper Menière's time, detailed history taking remains the first and most important diagnostic tool for MD as at present no 'gold standard' test exists. In order to limit the number of differential diagnoses, differentiation between vertigo and dizziness may be of clinical use.

Vertigo, according to the AAO-HNS [9] definition of vertigo spells in MD, involves a spinning sensation or illusory motion of the self or the environment. Dizziness, on the other hand, is less specific and is described by sensations of light-headedness, giddiness, wooziness or impending faint.

In addition to the distinction between dizziness and vertigo, the type of presentation may be of help to further differentiate between the cause of the complaints. The type of presentation can be divided into 1) a single acute episode of vertigo (not applicable to patients with MD by definition), 2) recurrent or episodic vertigo, 3) positional vertigo or 4) chronic sensations of dizziness or unsteadiness [53].

Diseases which manifest themselves with recurrent and spontaneous attacks of vertigo may particularly present diagnostic challenges when diagnosing MD due to similarity in medical history.

The most common cause of recurrent spontaneous vertigo is vestibular migraine (VM) (migrainous vertigo or migraine-associated vertigo) which affects about 30-50% of all patients with migraine [54,55]. Although complaints of vertigo and migraine commonly coincide, the Bárány Society only recently established a set of diagnostic criteria for VM which were added into the International Classification of Headache Disorders [56, 57].

Next to VM, there is a subgroup of patients who have attacks of recurrent vertigo without migrainous symptoms or cochlear features also known as benign recurrent vertigo. In 1981, Leliever and Barber were the first to describe this clinical syndrome as Recurrent Vestibulopathy (RV) [58]. RV, now renamed as 'Benign Recurrent Vertigo' (BRV), is characterised by recurrent spontaneous attacks of vertigo lasting for minutes to hours without any additional neurological or cochlear symptoms. Since additional symptoms are absent during attacks in RV, it may be regarded as a separate entity. However, previous studies claimed that RV might be related to either vestibular migraine or MD [59,60]. In **Chapter 5** the clinical characteristics of MD, VM and BRV will be explored and it will be assessed whether clinical symptoms exist to discern between these disorders.

Excluding differentials

Additional diagnostic assessments are important to increase or decrease the likelihood of the diagnosis and to exclude differentials. Excluding differentials should be based on prevalence rates.

In case laboratory evaluation is performed, one aims to rule out thyroid disorders, syphilis, anaemia, leukaemia, diabetes mellitus, immune or genetic disorders [61] whereas Magnetic Resonance Imaging (MRI) of the brain or the cerebellopontine angle is advised to eliminate central pathology, most importantly acoustic neuromas [62].

Vestibular function

The function of the vestibular system is generally assessed by the caloric test. In MD, the caloric test may reveal unilateral vestibular hypofunction [63], yet test results may fluctuate over time and normal results can be found as well [64-66]. Recently, the video-head impulse test (vHIT) was introduced [67] which assesses the vestibulo-ocular reflex based on unpredictable passive, high frequency head rotations. Little is known about the diagnostic accuracy of the vHIT in determining vestibular hypofunction when caloric testing is considered the reference standard. This will be the focus of **Chapter 6**. In previous research with the vHIT and MD, normal test results were found at least in the early stages of the disease [68,69]. The vHIT test results in later stages of the disease will be evaluated in **Chapter 7**.

Therapy

The main aim of treatment in MD is to reduce the frequency and intensity of the vertigo attacks and at the same time to preserve hearing and vestibular function [70]. Psychological suffering and reduced quality of life are linked to MD since disabling vertigo attacks can occur without warning [71,72]. Therefore, an effective prophylactic treatment is necessary to improve the quality of life of MD patients. Current pharmacological treatment options include betahistine, diuretics, oral steroids or intratympanic application of corticosteroids, and intratympanic gentamicin [73]. However, evidence in terms of reducing vertigo complaints has never been conclusive [74-76], except for intratympanic gentamicin treatment [77].

Of these pharmacological treatment options, betahistine is most commonly used, especially in Europe [78]. Betahistine has been available since 1968 and it is estimated that over 130 million people worldwide have used the drug [79]. Although it is thought to be specifically effective as medical treatment in MD, a Cochrane review [74] conducted in 2001 stated that there was no evidence of a benefit from the use of betahistine in this population. However, many studies have been performed since, and reassessment of the effect of betahistine in treating MD is therefore now warranted since it is still widely prescribed as first line

treatment for MD. **Chapter 9** describes the results of a systematic review examining the potential beneficial effect of betahistine for MD.

Non-pharmacological treatment includes positive pressure therapy (the Meniett device), ablative surgery such as vestibular nerve section, labyrinthectomy, endolymphatic sac surgery and VR [70,73,81]. Similar to the pharmacological treatment modalities, high quality evidence is also lacking for non-pharmacological therapies [80,81]. Since so many treatments exist without conclusive results, it may be hard for clinicians to select the best available treatment and to advise patients. **Chapter 10** portrays a protocol for an umbrella systematic review to summarise the body of evidence regarding treatment modalities in MD. In **Chapter 11** the results of this umbrella systematic review will be presented.

THESIS OUTLINE

The aims of this thesis are to explore the clinical aspects, to evaluate diagnostic tests and to systematically review the evidence for the effect of interventions for Menière's disease (MD). Part I describes the age of onset, second causes of dizziness in MD patients and compares clinical symptoms in patients with MD, Vestibular Migraine and Benign Recurrent Vertigo. Part II evaluates the diagnostic value and aspects of the vHIT in MD. Lastly, part III systematically summarizes the effect of treatment for MD based on current available literature. The main outcomes of the studies performed are summarized in the general discussion. Based on these outcomes, implications for clinical practice are stated and directions for future research are provided. The aim of this thesis is to answer the following research questions:

Part I.

Evaluation of clinical aspects of MD

- What is the age of onset in patients with MD in a specialized dizziness clinic in the Netherlands and is there a shift in age of onset (**Chapter 2**)?
- Which other causes of dizziness are prevalent alongside MD and do differences exist in specific age groups (**Chapter 3** and **Chapter 4**)?
- What are the clinical characteristics of patients with Benign Recurrent Vertigo, Vestibular Migraine and MD and can distinctive clinical symptoms be identified (**Chapter 5**)?

Part II.

Evaluations of diagnostic tests for MD

- What is the diagnostic value of the vHIT in determining vestibular hypofunction when compared to the caloric test in dizzy patients (**Chapter 6**)?
- Are vHIT test results in patients with MD more often normal in the early stage of the disease than at later stages (**Chapter 7**)?

Part III.

Evaluation of interventions for MD

- What is the effect of vestibular rehabilitation in patients with MD (**Chapter 8**)?
- What is the effect of betahistine in patients with MD (**Chapter 9**)?
- What is the most effective treatment for MD? (**Chapter 10** and **11**)?

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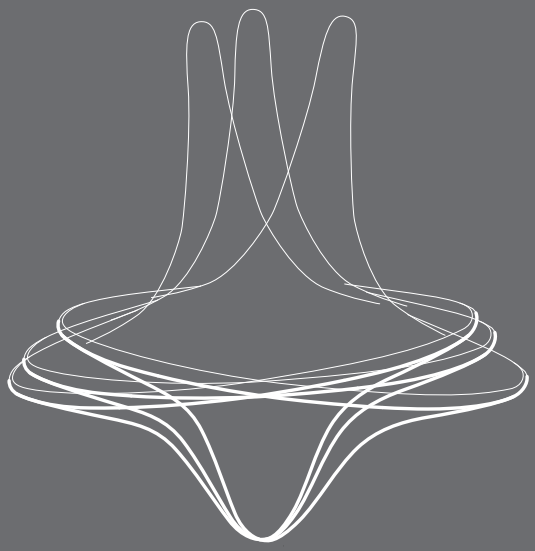
PART I

EVALUATION OF CLINICAL ASPECTS OF MENIÈRE'S DISEASE



2

AGE OF ONSET OF MENIÈRE'S DISEASE IN THE NETHERLANDS: DATA FROM A SPECIALISED DIZZINESS CLINIC

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ABSTRACT

Objective: To determine the age of onset of Menière's disease (MD) in patients who visited a specialized dizziness clinic. The second aim was to verify if the trend of a delayed age of onset of MD as reported for the Japanese population also occurs in the Netherlands.

Methods: We performed a retrospective data analysis of patients diagnosed with 'definite' Menière's disease who had visited our clinic between January 2000 and December 2013.

Results*:* Mean age of onset among the 296 MD patients was 53.0±14.1 years; 209 (71%) patients were diagnosed between the fifth and seventh decade of life. No trend towards a later onset of MD was found (regression coefficient ß: 0.03 for year of presentation; 95% confidence interval CI -0.34 to 0.61; p=0.58).

Conclusions*:* MD has a peak incidence between 40 and 69 years. We did not find a shift towards a later age of onset of MD.

Keywords*:* Menière's disease, age of onset, classification

INTRODUCTION

Patients with Menière's disease (MD) typically suffer from recurrent spontaneous episodes of vertigo, fluctuating hearing loss, tinnitus and aural fullness [1]. However, clinical symptoms vary widely and most findings are subjective and not specific. In the absence of diagnostic a 'reference' standard, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) has defined a set of diagnostic criteria for MD, which were originally published in 1972 and have been updated in 1995 [2]. The age of onset of MD symptoms is variable but generally the peak incidence lies in the fourth and fifth decade of life [3,4] as well as the seventh decade of life [5]. Recently, a 24-year retrospective survey in Japan [4] reported a progressive increase in the age at which MD manifests itself. This progressive shift towards a later age of onset is explained by the increase of the working elderly population, suggesting that work-related stress attributes to the development of MD [4,6]. To the best of our knowledge studies on the age of onset of MD in the Netherlands are lacking. As a result it is unknown whether a similar shift in age of onset towards an older age is also present in the MD population in the Netherlands.

In 2000, a multidisciplinary out-patient clinic for patients suffering from dizziness was established, the Apeldoorn Dizziness Centre (ADC). We retrospectively determined the age of onset in patients diagnosed with MD. Secondly, we analysed if there is evidence for a delay in the age of onset during the past 14 years in MD patients who visited our dizziness centre.

MATERIALS AND METHOD

Patients visiting the ADC between January 2000 and December 2013, and who were coded as having MD, were selected from our database. Data were analysed anonymously and under the supervision of the medical staff. The AAO-HNS diagnostic criteria for MD were used (see Table 1) [2]. No histopathological confirmation was sought in patients meeting the criteria for the diagnosis 'definite' MD, therefore we did not use the diagnosis 'certain' MD. A single attack of vertigo accompanied by unilateral hearing loss was regarded to be clinically more compatible with (viral) labyrinthitis, and therefore patients matching the criteria of 'probable' MD were not included into this analysis. 'Possible' MD represents a less well defined clinical entity and this population may as well contain vertigo related diseases (e.g. vestibular migraine) [7,8]. Therefore we only included patients with 'definite' MD in this retrospective analysis. Patients' data included sex, age, disease code, and dates of visit and referral status. Onset age, MD classification and unilateral or bilateral involvement were determined from the medical information processed in the electronic data handling system. In addition, we analysed audiometric test results, letters from the referring General Practitioner or specialist and discharge letters. The year at which vestibular and/

or audiological symptoms started was used to calculate the age of onset. The age of onset was classified as unknown if insufficient information was available, e.g. if the medical history was described as 'suffering from MD for many years'. We calculated the average degree of hearing loss (frequencies 0.5,1,2,4,6,8 kHz) and a low-Fletcher Index (FI low: mean over the frequency range 0.5 to 2 kHz) as measured by pure tone audiometry (PTA) [9]. The checklist for retrospective database studies reported by the International Society for Pharmacoeconomics and Outcomes Research was used as a guideline [10].

TABLE I

AAO-HNS 1995 CRITERIA FOR MÉNIÈRE'S DISEASE [2]

Certain Ménière's disease
– Definitive Ménière's disease
– Histopathological confirmation
Definite Ménière's disease
– ≥2 definitive spontaneous vertigo episodes of 20+ mins duration
– Audiometrically documented hearing loss on 1 occasion
– Tinnitus or aural fullness in treated ear
– Other causes excluded
Probable Ménière's disease
– 1 definitive spontaneous vertigo episode of 20+ mins duration
– Audiometrically documented hearing loss on 1 occasion
– Tinnitus or aural fullness in treated ear
– Other causes excluded
Possible Ménière's disease
– Episodic vertigo of Ménière's disease type, without hearing loss, or,
– Fluctuating or fixed SNHL, with disequilibrium but with no definitive episodes
– Other causes excluded

AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery; mins = minutes; SNHL = sensorineural hearing loss

Statistical analysis

We calculated frequencies for sex and bilateral involvement. Means and standard deviations were calculated for the PTA results and the age of onset for the 'definite' MD cases. Differences between groups were assessed by cross-tabulation and carried out using the chi-square test and *t*-test. To assess the relation between the year of presentation and the age of onset, we visually inspected the data and graphs and, if a linear trend was observed, univariate linear regression was used to assess the strength of the relationship. A p-value of less than 0.05 was considered significant. SPSS (version 20) was used for performing the statistical analyses.

RESULTS

Among a total of 7756 patients who had visited the ADC in the study period, 469 (6%) patients were identified as MD. Of these patients, 67% (n=314) met the criteria for 'definite' MD as defined by the AAO-HNS. Slightly more women (n=169, 53%) than men (n=145, 47%) were diagnosed with 'definite' MD. Six out of these 'definite' MD patients (2%) had bilateral involvement; in two patients we could not define if the disease was unilateral or bilateral. In both patients the attacks of vertigo had started only a few months before the visit and they suffered from tinnitus in both ears. Since these patients had previously experienced hearing loss, we could not determine which ear was affected. In the patients with unilateral 'definite' MD, the average hearing loss was 39±14.6 dB and the low-Fletcher index was 40.0±14.7 dB.

We could not determine the age of onset of MD in 18 (6%) patients. The mean age of onset of the included patients (n=296) was 53.0±14.1 years (Figure 1). Most patients (n= 209, 71%) had their first symptoms of MD in the fifth, sixth or seventh decade.

Both visual inspection and linear regression analysis revealed no relationship between the year of consultation at the ADC and the age of onset (regression coefficient ß: 0.03 for year of presentation; confidence interval -0.34 to 0.61; p=0.58) (**Figure 2**).

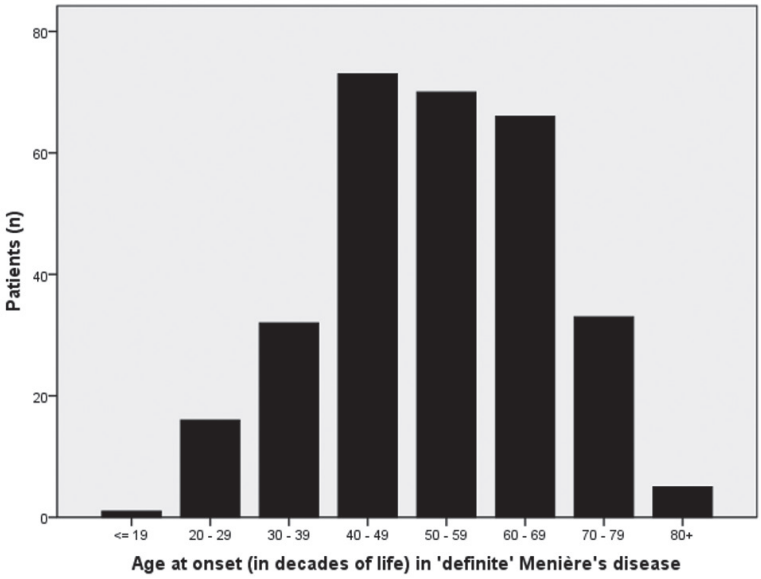

Figure 1. Age of onset of 'definite' Menière's disease.

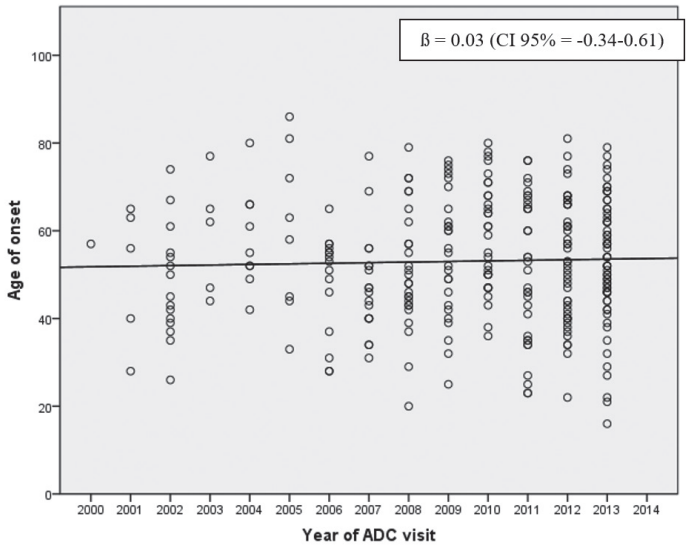

Figure 2. Scatter plot showing the correlation between year of ADC visit and age of onset. There is no linear relationship between the independent variable, i.e. year of ADC visit, and the dependent variable, i.e. age of onset exists (regression coefficient ß: 0.03 for year of presentation; 95% confidence interval CI -0.34 to 0.61; p=0.58).

DISCUSSION

This study aimed to investigated the age of onset in 'definite' MD patients who visited a specialized dizziness centre in the Netherlands from 2000 thru 2013. The peak incidence was found in the fifth to seventh decade of life, which is in line with previous publications [3-5, 11]. Our results do not support the suggestion of a progressive delay in age of onset in MD as reported by Shojaku et al [4]. Several factors may explain our contradictory results. First and foremost, the population aged ≥65 years grew more extensively and more rapidly in Japan than in the Netherlands. Based on Stattline rates [12] the Japanese population increased by 10.6% during the period 2000-2013 (from 25.5% to 36%). During the same period, the Dutch population grew only by 3.0%, from 20% to 23%. The population aged ≥65 years is smaller in the Netherlands and increase of this group was less extensive, and this may explain the absence of a trend for a forward shift in the peak incidence. Second, work-related fatigue inducing delayed onset of the disease does not apply to the Dutch population. The percentage of working elderly is significantly smaller in the Netherlands than in Japan, in the year 2000 this percentage numbered 6% [10] and 22% [4], respectively. Parallel to the increase of the population aged ≥65 years, the percentage of working elderly

grew only by 3% in the Netherlands 2000-2010 [13]. Although the life span considerably increased in Japan [12], it remains disputable to which extent work-related stress could cause the later onset of MD. Third, Shojaku *et al.*[4] performed a retrospective analysis based upon a 24-year survey starting in 1980. Our data registration started in 2000 and covered a period of only 14 years. The trend for a shift in onset of disease towards a later age could have already taken place prior to our study or our time window might have been too narrow to elicit a shift in age of onset. Finally, the Japanese Society for Equilibrium Research (JSER) criteria for MD published in 1988 considerably differ from those of the AAO-HNS 1995. When applying the JSER criteria, a threshold shift of >10 dB for the frequencies between 0.5 and 2 kHz as compared to the contralateral side, is required for the diagnosis of unilateral 'definite' MD. Consequently, 'possible' MD patients according to the AAO-HNS 1995 criteria might have been included as 'definite' MD patients in the Japanese study. In our study males and females appeared to be equally affected. This is in line with findings in the USA and Italy [3,5].

Bilateral involvement amounted to only 2% in the present study whereas previous studies reported involvement in 2 to 72% of the patients [14]. For instance, Huppert *et al.* reported bilateral involvement in up to 35% of the MD cases within 10 years [15]. Disparities in the frequency of bilateral involvement between studies may be explained by variation in diagnostic criteria and duration of disease at the time of study participation [14]. Bilateral MD rarely starts in both ears simultaneously but rather consecutively, in cases of long-standing disease [14,15]. One should bear in mind that our retrospective study design should be regarded as a less favourable method to analyse this variable and prospectively longitudinal assessments were not carried out.

The findings of this study further underscore that several problems are encountered when investigating the age of onset of MD. The onset of disease may be monosymptomatic, i.e. spells of vertigo only whereas the manifestation of other symptoms may be evident after months to several years [16]. This makes it difficult to determine the exact age at which the complete triad of symptoms starts. Furthermore, fluctuation of hearing loss can be particularly present in the early stage of the disease [17]. As the diagnostic criteria for MD were redefined over time and may vary between continents, establishing the age of onset in MD can be a complex undertaking.

We investigated the age of onset in MD patients in the Netherlands. MD is generally diagnosed in the fifth to seventh decades of life and onset of disease at a later age is uncommon. We did not find a trend for a forward shift of peak incidence of MD. A generally accepted and uniform set of diagnostic guidelines as to how to report epidemiological MD characteristics is required for comparison of research data. A prospective population-based study is recommended to identify actual incidence and prevalence rates as well as rates of bilateral involvement in Dutch MD patients.

ACKNOWLEDGEMENT

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The age of onset of Menière's disease in the Netherlands was investigated
Menière's disease generally manifests itself in the fifth to seventh decades of life
No trend for an increase of onset of disease at an older age was found
Bilateral involvement occurred in 2% of the Menière's disease population

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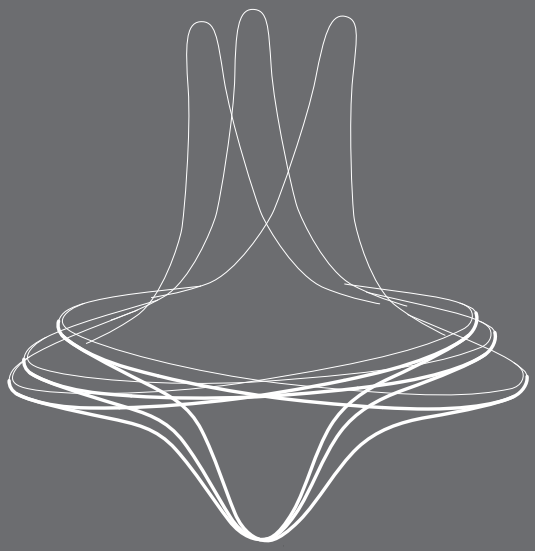

3

TWO COMMON SECOND CAUSES OF DIZZINESS IN PATIENTS WITH MENIÈRE'S DISEASE

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ABSTRACT

Objective: There are no epidemiological studies quantifying the prevalence of second causes of dizziness in Menière's disease (MD). Therefore, we aimed to quantify which dizziness-inducing causes are prevalent alongside MD. Moreover, we analysed which second cause of dizziness was more common in a specific age group and if age was a risk factor.

Study design: Retrospective cohort study.

Setting: Tertiary referral center.

Methods: Data were retrospectively obtained from all MD patients who visited our clinic between January 2000 and December 2013. Workup included vestibular tests, pure tone audiometry, blood pressure monitoring, and the hyperventilation provocation test, the Nijmegen Questionnaire and the Hospital Anxiety and Depression Scale. The final causes of dizziness were based on consensus between an ENT-surgeon and a neurologist who were consulted simultaneously.

Results: We found that 143 (30%) of 469 MD patients suffered from a second cause of dizziness. The two most common causes were Psychological Distress (PD) (70%) and Benign Paroxysmal Positional Vertigo (BPPV) (18%). The mean age for MD patients with PD was 58.7±13.3 years compared to the mean age of 63.9±14.3 years for MD patients without PD (mean difference=-5.2 years, 95% CI:-8.3 to -2.2, p=0.001). MD patients younger than 60 of age had a 15% higher risk of suffering from psychological distress than those who were older than 60 (risk difference 15%, 95% CI 7.0%-22%). Age could not be identified as a risk factor for BPPV in older MD patients.

Conclusions: In 30% of the patients with MD a second cause of dizziness is present. PD most commonly coincides with MD, especially in younger patients. The second most common cause is BPPV.

Key words: Menière's disease, comorbidity, diagnoses, dizziness.

INTRODUCTION

Spontaneous episodes of vertigo accompanied by hearing loss, tinnitus and aural fullness are hallmark characteristics in patients suffering from Menière's Disease (MD). However, as clinical symptoms vary widely and most of these symptoms are subjective and not specific, the disease can present diagnostic challenges. In 1995, a set of criteria for the diagnosis of MD was established by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [1]. Taking into account that a reference diagnostic standard and a confirmatory test are still absent, a detailed medical history is essential. Therefore, MD is a clinical diagnosis. The diagnostic process is further complicated when multiple diagnoses causing dizziness coexist. During the first clinical visit and also during follow-up, coexisting causes may obscure the diagnosis MD and challenge the physician to clarify the origin of complaints.

While previous studies demonstrated that Benign Paroxysmal Positional Vertigo (BPPV) is associated with orthostatic hypotension [2], MD commonly coincides with BPPV [3-5] and psychological distress (PD) [6,7]. PD, unpleasant experiences of emotional or psychological nature such as anxiety or depression, is known to be prevalent in patients with chronic dizziness [8], especially in patients with MD [9].

However, the previously mentioned studies assessed the prevalence of a single diagnosis within MD populations. To date, it is unknown which second causes of dizziness are most common in patients with MD. In the present study, we aimed to quantify the prevalence of the second causes of dizziness in patients with MD who visited our tertiary dizziness clinic. In line with previous literature on general dizziness populations, PD tends to be more common in the younger dizzy patient [6,9] whereas BPPV becomes more prevalent at an older age [3]. However, as prevalence rates of PD and BPPV alongside MD are unknown, the second objective was to establish whether comparable age differences also existed in patients with these second causes of dizziness in presence of MD.

MATERIALS AND METHODS

We obtained records from all the MD patients in our database who had visited our centre between January 2000 and December 2013. Patients were included if they met the AAO-HNS 1995 criteria for 'definite' and 'possible' MD (see **Table 1)** [1]. Based on the medical information processed, we assessed if the selected MD patients suffered from two different types of dizziness, such as 'episodic vertigo' and 'positional vertigo' or 'episodic vertigo' and 'chronic sensations of light-headedness'. We analysed anonymous data on a second cause of dizziness based on the medical information as recorded in the electronic data handling system and in discharge letters.

All procedures were in accordance with the ethical standards and in line with the Helsinki declaration. All data were analysed anonymously. In all patients, the workup included vestibular tests (oculomotor, caloric, rotational and positional), pure tone audiometry, and blood pressure monitoring. In addition, the hyperventilation provocation test was performed and two questionnaires were filled in prior to the clinical visit.

TABLE 1. Criteria for Menière's disease published by the American Academy of Otolaryngology-Head and Neck Surgery in 1995[1].

Certain Menière's disease	Definitive Menière's disease
	Histopathological confirmation
Definitive Menière's disease	Two or more definitive spontaneous episodes of vertigo of 20 minutes or longer
	Audiometrically documented hearing loss on one occasion
	Tinnitus or aural fullness in the treated ear
	Other causes excluded
Probable Menière's disease	One definitive spontaneous episode of vertigo of 20 minutes or longer
	Audiometrically documented hearing loss on one occasion
	Tinnitus or aural fullness in the treated ear
	Other causes excluded
Possible Menière's disease	Episodic vertigo of the Menière type without hearing loss or,
	Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes
	Other causes excluded

The hyperventilation provocation test

During the hyperventilation provocation test (HVPT), hypocapnia was induced by having the patient overbreath intentionally for several minutes. Immediately following the HVPT, the patient was asked if any symptoms similar to what they had experienced before occurred during the test. The test was considered positive if such symptoms were present [10].

The Nijmegen questionnaire and Hospital Anxiety Depression Scale

Patients were asked to complete two questionnaires prior to the clinical visit: the Nijmegen Questionnaire (NQ) and the Hospital Anxiety and Depression Scale (HADS) (from 2012 onwards). The NQ is a valid method to screen for the hyperventilation syndrome (HVS) [11,12].The questionnaire consists of 16 items, which are graded as follows: 0=never

occurring, 1=rare, 2=sometimes, 3=often, 4=very often. A total score higher than 23 out of 64 is suggestive for a diagnosis of HVS.
The HADS is an instrument for screening for PD [13]. It has been shown to be a reliable and valid tool for evaluating patients in various disease populations [14]. The HADS contains 14 items: an anxiety subscale and a depression subscale, both consisting of 7 items. Items have the same answering options as the NQ. We considered the test results positive if a score of ≥ 8 on either subscale (anxiety or depression) was found in the presence of complaints of 'light-headedness' or 'giddiness' [13,15].

Definitions of the causes of dizziness

A positive test result for either the HVPT or the NQ was considered to be suggestive for HVS. HVS is defined as a syndrome characterized by various somatic symptoms which cause "physiologically inappropriate hyperventilation and are usually reproduced by voluntary hyperventilation" [16]. Symptoms of HVS have been proven to be correlated with increased levels of anxiety and depression [17,18]. Similarly, chronic vertigo disorders – including MD – are known to be associated with PD complaints [12,19]. As a result, MD patients with increased scores on the HVPT, the NQ or the HADS were clinically suspected of having PD. In line with the definition of the National Comprehensive Cancer Network, PD was considered a multifactorial unpleasant emotional experience of a psychological or social nature [20].

We used current available diagnostic criteria to confirm vestibular neuritis [21], vestibular migraine [22], and Benign Paroxysmal Positional Vertigo (BPPV) [23]. The diagnosis of BPPV was established by complaints of episodic vertigo with changes in head position and the presence of a characteristic nystagmus provoked by either the Dix-Hallpike manoeuvre or the supine roll test. The BPPV group also included patients with subjective BPPV. In these patients a diagnostic manoeuvre provokes vertigo, but not a nystagmus. Historical BPPV was diagnosed when a patient had typical complaints of positional vertigo but a negative Dix-Hallpike manoeuvre at the time of evaluation. Since subjective and historical BPPV are less clearly defined, these patients were excluded from analysis.
Conventional open bithermal loop caloric testing (33°C and 44°C) was used in both ears to elicit vestibular responses. The Jongkees formula [24] was applied to express the vestibular preponderance (VP) and directional preponderance (DP) in percentages, based on the velocity of the slow phase component of nystagmus evoked by each vestibular organ. Vestibular hypofunction was defined as a vestibular preponderance of 22% or more or a directional preponderance of 28% or more [25,26]. Caloric testing was also considered abnormal if the responses for all irrigations were below normal. The criterion for bilateral weakness was a V_{max} below 15°/s for each vestibular organ (V_{max} is the sum of the slow-phase velocity for irrigation warm water + slow phase velocity for irrigation cold water).

Orthostatic hypotension was defined as a reproducible fall in systolic blood pressure of 20 mmHg or diastolic blood pressure of 10 mmHg during the first 2 minutes standing. We diagnosed patients with a central vascular disorder on the basis of clinical history and abnormal findings on neurologic and MRI examinations. The clinical diagnoses were determined by an ENT-surgeon and a neurologist by means of simultaneous consultation.

Statistical analysis

By means of SPPS software (version 18), we calculated frequencies for categorical variables, including sex, type of MD and the second causes of dizziness. Means and standard deviations were calculated for age. MD patients with a common second cause were grouped and compared to patients without these causes. In the analysis of the BPPV group, we excluded patients with historical or subjective BPPV. Cut-offs for age were based on previous literature: young adults were defined as ≤ 60 years of age; old adults were defined as >70 years of age [27]. Differences were assessed by using the *t*-test and chi-square test. Absolute and relative risk ratios were calculated with the online software of Open Source Epidemiologic Statistics for Public Health (available at (www.openepi.com). A p level below 0.05 was considered significant.

RESULTS

The 469 MD patients included in this study consisted of slightly more women (n=254, 54%) than men. The mean age was 62.8±14.2 years. In 67% of cases (n=314) the diagnosis was 'definite' MD.

Second causes of dizziness

Table 2 shows the causes of dizziness of the included MD patients. The presence of another cause of dizziness was registered in 143 patients (30%). These patients comprised significantly more women (n=86, 64%) than men (n=49, 36%) (p=0.01). The mean ages for MD with a second cause of dizziness were comparable (62.2 ±14.1) to MD patients without (63.0 ± 14.2 years). As shown in **Figure 1**, the most common coexisting diagnoses were PD (n=102, 70%) and BPPV (n=24, 18%). In 15 (11%) patients in the BPPV group, a typical nystagmus was provoked by either the Dix-Hallpike manoeuvre or the supine roll test.

Age in MD patients with and without PD

MD patients with PD (n=102) were compared with MD patients without this diagnosis (n=367). The mean age for MD patients with PD was significantly lower (59.3±13.3 years) than in MD patients without PD (63.6±14.3 years) (mean difference=-4.2 years, 95% CI:-7.5 to -1.0, p=0.01). In line with **Table 3**, MD patients younger than 60 years of age had a

15.4% (95% CI: 11.5-20.3) higher risk of suffering from PD than patients above 60 years of age. This correlated with a relative risk ratio of 2.0 %(95% CI:1.4-2.8).

TABLE 2. Coexisting diagnoses in the MD population.

Diagnosis	**Number (%)**
No coexisting diagnosis	326 (69.5)
PD*	102 (21.7)
BPPV†	15 (3.2)
Orthostatic hypotension (incl. asymptomatic)	7 (1.5)
Vestibular migraine	5 (1.1)
Cardiovascular	3 (0.6)
Unknown central cause	1 (0.2)
Bilateral vestibular paralysis	1 (0.2)
Total	**469(100)**

*=Psychological distress; †= Benign Paroxysmal Positional Vertigo

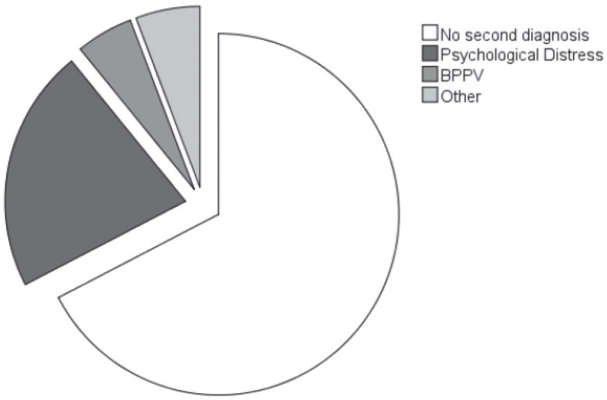

Figure 1. Most common second diagnoses in Menière's disease patients (N=469)

TABLE 3. Absolute and relative risks for young adult MD patients with psychological distress.

	MD with PD*	MD	Total
Age ≤60	61	142	203
Age >60	41	225	266
	102	367	469

*PD= Psychological Distress. MD patients younger than 60 year of age had a risk of 30.1% (95% CI:24.2%-36.7%) for psychological distress. This risk was 15.4% (95% CI:11.5%-20.3%) in older MD patients. The absolute risk difference was 14.6% (95% CI: 6.9%-22.3%). The relative risk ratio was 1.95 (95% CI:1.4%-2.8%).

Age in MD patients with and without BPPV

MD patients with proven BPPV had a mean age of 66.6±13.2 (n=15) whereas MD patients without BPPV were younger (62.6±14.2 (n=454); mean difference 4.0 years, 95% CI: -3.4 to 11.4, p=0.29). As displayed in **Table 4,** older age (> 70 years) was not found to be a significant risk factor in the development of BPPV in our MD population. The risk difference was 2.2 (95% CI: - 6.1.2 -1.6) and the relative risk ratio was 0.5 (95% CI:0.2-1.4).

TABLE 4. Absolute and relative risks for old adult MD patients to suffer from BPPV.

	MD with BPPV*	MD	Total
Age ≤70	8	313	321
Age >70	7	141	148
	15	454	469

*= Benign Paroxysmal Positional Vertigo, patients with historical or subjective BPPV were excluded. MD patients > 70 years had a risk of 4.7%(95% CI:2.1%-9.6%) to suffer from BPPV. This risk was 2.5% (95% CI:1.2%-49%) in MD patients ≤ 70 years. The absolute risk difference was 2.4% (95% CI: -6.1%-1.6%). The relative risk ratio was 0.6% (95% CI:0.2%-1.4%).

DISCUSSION

To date, there are no epidemiological studies quantifying the prevalence of second causes of dizziness in MD. In the present study, we aimed to determine the prevalence of secondary causes of dizziness in patients with MD. Additionally, we aimed to verify whether MD patients with PD were younger and if MD patients with BPPV were older than patients without these second causes of dizziness.

In our retrospective analysis of 469 MD patients, a second cause of dizziness was found in almost one third of the population. The two most second causes of dizziness were PD and BPPV. In line with our hypothesis, MD patients with PD were significantly younger and the

risk of PD comorbidity was 15% higher in younger MD patients. MD patients with BPPV were slightly, although not statistically significantly older than MD patients without BPPV. Our results on elevated anxiety and depression scores in MD patients were comparable to analyses of PD in the general population and in various disease populations. An analysis of the general German population revealed that the HADS scores were increased (≥8) for anxiety in 21% of the subjects and for depression in 23% [15]. In previous studies among patients with sarcoidosis (28) and systemic lupus erythematodes [29] elevated HADS scores for anxiety and depression ranged from 16% to 39%. In a study of patients with different types of vestibular peripheral vertigo, the prevalence rate of anxiety and depression in patients with MD was more or less the same as in patients with vestibular migraine [30]. Although high levels of anxiety and depression are commonly linked to MD [6,7,31], the presence of PD may be less distinctive for MD than previously thought.

No reports were found assessing age differences within MD populations based on PD. However, our finding is in line with previous literature in general dizziness populations that patients with both vertigo and PD tend to be younger than patients without these complaints [9].

The prevalence of BPPV in the general population lies between 10 to 64 per 100.000, with a lifetime prevalence of 2.4% [23,32]. Previous literature demonstrated an association between MD and BPPV [33,34]. Endolymphatic hydrops may damage the utricle, which may cause loosening of otoconia, resulting in BPPV [35]. In concordance with previous studies, we found a significantly higher prevalence of 5% BPPV in our MD population. However, previous research found BPPV prevalence rates up to 30% [2,3,34]. This discrepancy may be accounted for by the difference in study design. Taura *et al.* [33] prospectively registered BPPV-like vertigo episodes during a follow-up period of up to 30 months whereas we used a retrospective approach and assessment at a single clinical consultation. Therefore, we may have underestimated the BPPV prevalence in our population.

In our study, BPPV patients were older than MD patients without BPPV, but no statistical significance was found. This finding is unexpected, as previous reports show that BPPV becomes increasingly prevalent in older patients [2,23]. Since only 15 proven BPPV patients could be analysed in this subgroup, it might be due to chance that current results were found.

What emerges from the current study is the need to take PD and BPPV into account when considering therapy options in MD. Patients with PD alongside MD may benefit from psychological therapy. Although psychological interventions are generally not regarded as the key component of therapy in MD, cognitive behavioural therapy has been effective in treating vertigo and tinnitus [36]. When BPPV is encountered during follow-up, this can be treated effectively by canalith repositioning manoeuvres [11,35].

The scope of this study was limited in several ways. The most important potential limitation concerns the suspicion of PD based on the presence of HVS. Even though HVS was proven to be correlated with increased levels of PD, Hornsveld *et al.* [37] stated that the term HVS is best to be avoided in clinical practice. In addition, confirmation of a psychological disorder would require a structured clinical interview according to the DSM-IV-TR. We are aware that no complete psychological work-up was performed and we therefore not cannot calculate prevalence rates of anxiety and depression.

Moreover, the present study included patients who visited our centre between January 2000 and December 2013, whereas we did not use the HADS until 2012. Nonetheless, the number of patients who visited our dizziness centre increased substantially during the final two years of this study. Thirty percent (n=33) of the MD patients with PD were identified by increased levels on the HADS. In 10 patients PD was based on an elevated HADS score only. The remaining were identified by abnormality on the HADS and either the HVPT or the NQ. Due to this methodological inconsistency, it is likely that prevalence rates of PD would have differed in case we had used the HADS from 2000 onwards.

In MD, a second cause of dizziness is a common finding. In 30% of the patients we found a second cause of dizziness. The two most second causes are PD and BPPV which comprise 80% the patients with a second cause of dizziness. PD is especially common in younger MD patients, but the prevalence is comparable to various other disease populations. The current study emphasizes the need to take PD and BPPV into account when considering therapy options in MD.

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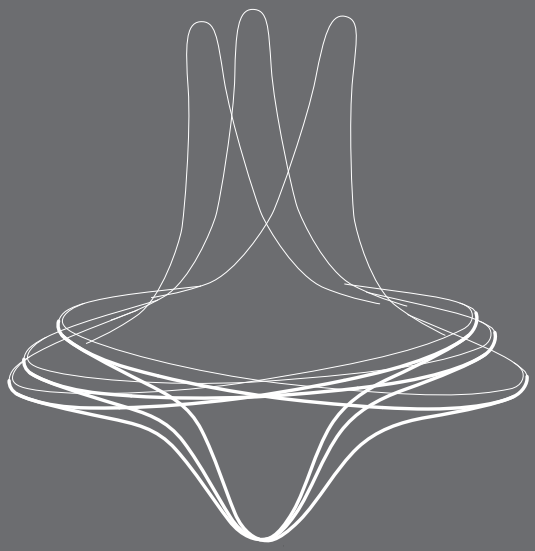

4

IN REPLY TO LETTER TO THE EDITOR: "TWO COMMON SECOND CAUSES OF DIZZINESS IN PATIENTS WITH MENIÈRE'S DISEASE"

Babette F. van Esch
Hester J. van der Zaag-Loonen
Tjasse D. Bruintjes
Peter Paul G. van Benthem

Otology and Neurotology 2017 Jul;38(6):921-922

In Reply: We highly appreciate the authors' interest in our study that evaluates second causes of dizziness in patients with Menière's disease (MD).

We agree that previous studies evaluated overlapping diagnoses in patients with MD which we mentioned in both the introduction and the discussion of the manuscript. Nonetheless, previous research investigated a single second cause of dizziness, whereas our study investigates multiple second causes of dizziness in patients with MD.

We understand the concern as to the references regarding psychological distress (PD). We are fully aware of the fact that it is difficult to determine the share of PD in the cause of dizziness. Therefore, we stated this to be the most important limitation of the study. However, the mere fact that such a high level of PD exists in patients suffering from MD suggests that PD might serve as an etiological factor. Nonetheless, we are fully aware that a psychological disorder associated with the presence of PD, such as an anxiety disorder or depression, should be diagnosed following the criteria and codes of the DSM-V[1].

With respect to the prevalence of vestibular migraine (VM), we agree that our rates are far lower than those in previous reports on this matter. Our retrospective study evaluated patients who visited our tertiary dizziness centre between January 2000 and December 2013. Only after the publication of the vestibular migraine criteria in July 2012 by Lempert *et al.* [2], we used the diagnosis VM on a larger scale. Thus, VM was only registered during a relative short time frame during the total study period, which might explain our lower prevalence rate. Moreover, we did not register migraine if a relation with vertigo symptoms was absent or unclear.

We hope these answers are helpful. Once again, thank you for your interest in our study.

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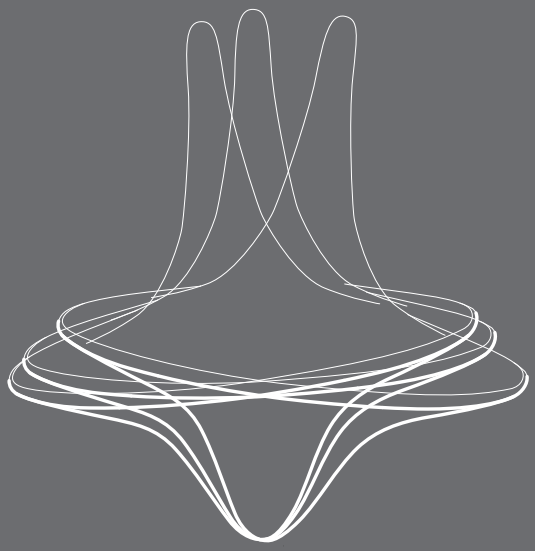

5

CLINICAL CHARACTERISTICS OF BENIGN RECURRENT VESTIBULOPHATHY: CLEARLY DISTINCTIVE FROM VESTIBULAR MIGRAINE AND MENIÈRE'S DISEASE?

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Erik van Wensen
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ABSTRACT

Objective: We aimed to systematically investigate the clinical characteristics of benign recurrent vestibulopathy (BRV), vestibular migraine (VM) and Menière's disease (MD) and to assess whether clinical symptoms exist that are unique to BRV.

Study design: Prospective cohort study.

Setting: Tertiary referral centre.

Methods: Between January 2015 and November 2016, patients were prospectively recruited at a specialised dizziness clinic. Patients were included if they met the diagnostic criteria for BRV, VM or MD which was evaluated by simultaneous consultation of an otorhinolaryngologist and neurologist. All patients received a comprehensive clinical examination which included vestibular tests and pure tone audiometry. A questionnaire was designed to systematically document symptoms of the three vestibular disorders.

Results: A total of 122 patients were included in our study, 65 (53%) were females in whom 29 (24%) were postmenopausal. The mean age was 55.5±13.7 years and the mean age of onset of vertigo attacks was 49.2±14.8 years (n=119). Forty-five (37%) patients had a clinical diagnosis of BRV, 34 (28%) of VM and 43 (35%) of MD. No symptom could be identified which was specifically linked to BRV. In patients with BRV, similar to those with VM, we found a female preponderance ($p=0.05$ in BRV, $p=0.001$ in VM). Patients with VM reported significantly more often a positive history of motion sickness ($p=0.01$). In addition, canal paresis was most profound in patients with MD ($p=0.001$).

Conclusions: We found no clinical characteristics which were distinctive for BRV. However, we did find several distinctive clinical features for VM and MD which may assist the physician in their history taking.

INTRODUCTION

In 1979, Slater first described the clinical syndrome of benign recurrent vestibulopathy (BRV) [1]. BRV is characterised by chronic recurrent spontaneous attacks of vertigo lasting from minutes to hours without cochlear or neurological symptoms. Since these symptoms are absent during vertigo attacks in BRV, it may be regarded as a separate entity. However, as high co-morbidity rates of migraine are found in patients with BRV it may be etiologically related to vestibular migraine (VM) [2,3]. On the other hand, a fraction of patients may develop unilateral hearing loss like in Menière's disease (MD) and therefore, BRV has been considered as a vestibular form of MD [4].

Recently, the diagnostic criteria for VM were established by the Bárány Society and added into the International Classification of Headache Disorders [5,6]. This was a result of the lack of a specific diagnosis in patients with both migraine and vestibular symptoms. The diagnostic criteria for definite VM (dVM) describe a patient who experiences spontaneous episodes of vertigo (minimum of five episodes) which are accompanied by migrainous symptoms (i.e. photophobia, phonophobia, unilateral headache) in at least 50% of the episodes. In addition, the patient has migraine or a history of migraine. Either a history of migraine or episodic vertigo accompanied by migrainous symptoms is sufficient for the diagnosis of probable VM (pVM).

Criteria for MD were defined by the American Academy of Otorhinolaryngology-Head and Neck Surgery (AAO-HNS) [7]. In MD, vertigo episodes should be accompanied by cochlear symptoms which include hearing loss, tinnitus and aural fullness.

Besides documented hearing loss by means of pure tone audiometry, no diagnostic reference standard or confirmatory test exists for BRV, VM or MD. All diagnoses are primarily based on a detailed and systematic history taking and discrimination between these diagnoses can be challenging as symptoms overlap [8,9].

In 2014, Lopez-Escamez *et al.* systematically investigated whether clinical features could be identified which best discriminated between VM and MD [10]. However, BRV was not included in these analyses. Identification of clinical characteristics that are proven to be distinctive for BRV may help the clinician to discriminate between BRV, VM and MD and may contribute to the debate over whether or not BRV can be regarded as a separate entity. The aim of the current study was to explore the clinical characteristics of BRV, VM and MD and to assess whether clinical symptoms exist that are clearly distinctive for one of these disorders.

MATERIALS AND METHODS

Population

Between January 2015 and November 2016, patients were prospectively recruited at the Apeldoorn Dizziness Centre (ADC). The ADC is a tertiary centre providing specialised care for patients suffering from dizziness.

The final clinical diagnosis was based on mutual consensus after simultaneous consultation of an otorhinolaryngologist and a neurologist. We included patients who fulfilled the syndrome description for BRV [1] as described by Slater: spontaneous vertigo attacks lasting from minutes to hours in absence of any neurological or cochlear symptoms. In addition, patients were included who met the diagnostic criteria for either dVM, pVM or definite MD [5]. The revised diagnostic criteria for MD were only published in 2015. However, as study recruitment started before publication of these revised criteria, we used the previously published diagnostic criteria [7]. We excluded patients who did not met the criteria for BRV, VM or MD. The diagnostic criteria of BRV, pVM, dVM and MD are shown in **Figure 1**. Additional exclusion criteria were other peripheral disorders such as Benign Paroxysmal Positioning Vertigo (BPPV) [10]. No pregnant and breastfeeding women were included in the current study.

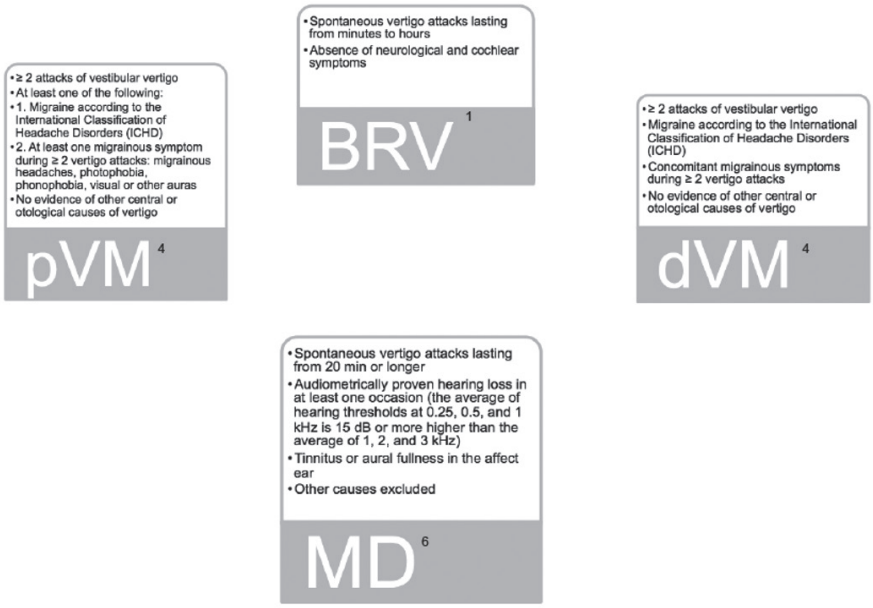

Figure 1. Diagnostic criteria for benign recurrent vestibulopathy (BRV), vestibular migraine (VM, definite and probable) and Menière's disease (MD).

Ethical considerations

The study was designed and conducted in compliance with the Helsinki Declaration. Approval of the local ethics committee was obtained and all data was analysed anonymously. All patients gave written informed consent before entering the study.

Methods

Prior to their appointment, patients were sent the Hospital Anxiety and Depression Score (HADS). The HADS is a self-rating questionnaire and is considered to measure psychological distress rather than to detect psychiatric comorbidity [11]. The HADS contains 14 items: an anxiety subscale and a depression subscale, both consisting of 7 items. A total score of ≥ 7 for one of the subscales was considered as an indication for psychological distress [12].

During their visit at the ADC all patients underwent comprehensive clinical examination and additional testing, which included a pure tone audiometry (PTA) and caloric testing. With regard to the PTA, bone conduction thresholds were examined on the frequencies 0.25 to 4 kHz. In line with the AAO-HNS 1995 guideline [7], the frequencies 0.5,1, 2 and 3 kHz were used to calculate mean hearing thresholds. Conventional open bithermal caloric testing with water (33°C and 44°C) in both ears was used to elicit vestibular responses. The Jongkees formula [13] was applied to express the vestibular asymmetry in percentages, based on the velocity of the slow phase component of nystagmus evoked by each vestibular organ. Based on the values used in previous research [13] and on our own experience, caloric tests were considered abnormal if the vestibular asymmetry was 22% or higher.

As mentioned earlier, the final diagnosis was based on simultaneous consultation of an otorhinolaryngologist and a neurologist. A questionnaire was designed to systematically document vertigo symptoms of the three vestibular disorders of interest (see the supplementary file and **Table 1**). Questions were formulated regarding the basic demographic characteristics (sex, age, menopausal state), the age of onset of disease, the vertigo attack frequency (last month, past 6 months), the characteristics of the vertigo attacks (the duration, nature and intensity), the clinical and family history (for presence of MD, migraine, motion sickness), additional symptoms during vertigo attacks including vegetative symptoms (nausea or vomiting), auditory symptoms, migraine related symptoms and psychological distress. Patients were asked if known factors existed that provoked onset of vertigo complaints and if concomitant medication was taken.

TABLE 1. Summary of structured questionnaire to record clinical symptoms associated with vertigo episodes of benign recurrent vestibulopathy (BRV), vestibular migraine (VM, definite or probable) and Menière's disease (MD).

	Predefined questions
Demographic characteristics	Sex, date of birth, menopausal state
History of vertigo attacks	Age of onset of vertigo attacks
Vertigo attack frequency	Past 6 months/ last month
Vertigo attack characteristics	Duration, nature of attack, intensity (*VAS-score)
Clinical history/family history	For migraine, Menière's disease, motion sickness
Additional symptoms during vertigo attacks	Vegetative symptoms (nausea, vomiting)
	Auditory symptoms (loss of hearing, tinnitus, aural fullness)
	Migraine related symptoms (visual aura (spots, stars, flashes), photophobia, phonophobia, migraine)
	Psychological distress (‡based on HADS evaluation)
Contributing factors provoking vertigo attacks	Stress, fatigue, menstrual cycle, food, alcohol intake, head movements, physical activity
Concomitant medication	Indication, total daily dose
Final clinical diagnosis matching current diagnostic criteria	

***** Visual Analogue Scale (0= no intense vertigo sensation, 10=most severe vertigo sensation), ‡ HADS= Hospital Anxiety and Depression Scale.

Statistical analysis

Statistical analyses were performed using SPSS software (version 23). Means and standard deviations were calculated for age and age of onset. We calculated frequencies for categorical variables including sex, the menopausal state, the characteristics of vertigo attacks, the clinical and family history, the presence of additional symptoms during vertigo attacks, factors which provoked onset of vertigo attacks and the clinical diagnosis. For skewed data (VAS-scores for vertigo intensity, PTA results, caloric test results and HADS results) median and ranges were calculated. Differences between groups were assessed by means of cross-tabulation and analysed using the chi-square test and the t-test. Differences between more than two groups for normally distributed data were analysed by means of one-way ANOVA; non-normally distributed data were analysed by means of the Kruskal Wallis test. A p level below 0.05 was considered statistically significant.

TABLE 2. Clinical characteristics of 122 patients with BRV, dVM, pVM or MD at initial presentation.

	BRV=45		pVM=18		dVM=16		MD=43	
	N	%	N	%	N	%	N	%
Sex, no. (%)								
Male	**20**	44	7	39	2	13	28	65
Female	**25**	56	11	61	14	88	15	35
Postmenopausal	13	52	4	36	5	36	7	47
Age (in years; mean (±*)	59.8±11.5		53.1±14.1		52.6±14.5		53.2±14.6	
Age of onset symptoms (in years; mean; ±)	51.8±14.2		43.8±17.3		47.4±14.3		46.5±14.3	
Vertigo attack frequency last 6 months								
<2 attacks	7	16	5	28	3	19	2	5
2-10 attacks	26	58	8	44	11	69	25	58
>10 attacks	12	27	5	28	2	13	16	37
Duration of vertigo attacks								
Minutes	12	27	7	39	3	19	6	14
< 24 hours	20	44	7	39	8	50	35	81
> 24 hours	13	29	4	22	5	31	2	5
Intensity of vertigo attacks VAS score (median, range)	10(4-10)		10(7-10)		9(4-10)		10(2-10)	
History of or continuing symptoms of motion sickness	10	22	11	61	10	63	13	30
Family history migraine	12	27	7	39	9	56	7	16
Family history MD	2	4	1	6	1	6	7	16
Additional symptoms during attacks								
Vegetative symptoms								
Nausea	38	84	17	94	16	100	39	91
Vomiting	27	60	12	67	7	44	32	74

TABLE 2. Continued.

		BRV=45		pVM=18		dVM=16		MD=43	
		N	%	N	%	N	%	N	%
Auditory symptoms									
Hearing loss	Symmetrical	23	51	15	83	12	75	0	0
	Asymmetrical	5	11	1	6	0	0	43	100
Tinnitus	Symmetrical	8	18	4	22	2	13	3	7
	Asymmetrical	5	11	3	17	2	13	39	91
Aural fullness	Symmetrical	3	7	1	6	1	6	1	2
	Asymmetrical	2	4	1	6	2	13	15	35
Migraine related symptoms									
Aura		0	0	4	22	7	44	10	23
Photophobia		0	0	7	39	11	69	17	40
Phonophobia		5	11	5	28	11	69	23	54
Migraine syndrome according to ICHD criteria		0	0	10	56	16	100	0	0
Non-migraine type headache		9	20	0	0	0	0	13	30
Contributing factors									
Stress		17	38	13	72	13	81	26	60
Menstrual cycle		3	7	2	11	3	19	2	4
Fatigue		15	33	11	61	10	63	21	49
Head movement		14	31	5	28	8	50	19	44
Alcohol		2	4	3	17	3	19	4	9

RESULTS

Demographic characteristics

A total of 122 patients were included in our study, 65 (53%) were females in whom 29 (24%) were postmenopausal. The mean age was 55.5±13.7 years and the mean age of onset of vertigo attacks was 48.2±14.8 years. Demographic and clinical characteristics are presented in **Table 2**. With respect to the vertigo attack frequency and the duration of vertigo attacks no statistically significant differences between BRV, VM and MD patients could be demonstrated.

Clinical characteristics of BRV

Forty-five (37%) patients had a clinical diagnosis of BRV with a mean age of 59.8±11.5 years and a mean age of onset of 51.8±14.2 years. Patients with BRV were significantly older at inclusion compared to patients with VM or MD (one-way ANOVA p=0.03). No differences were found with respect to age of onset of symptoms. The population consisted of 25 (56%) women of whom 13 (29%) reported to be postmenopausal. The proportion of women was significantly higher in BRV patients than in MD patients (p=0.05) but comparable to that in the VM group (p=0.1). We found non-migraine type headache in 9 (20%) patients with BRV and no neurological migraine-related symptoms.

Clinical characteristics of pVM and dVM

Eighteen (15%) patients had a clinical diagnosis of pVM and 16 (13%) of dVM. The mean age and age of onset was 53.1±14.1 and 43.8±17.3 in pVM patients. dVM patients had a mean age of 52.6±14.5 and a mean age of onset of 47.4±14.3 years. The highest proportion of women was found in these two subgroups: 11 (61%) in case of pVM and 15 (88%) in case of dVM, respectively. Similar to BRV, significantly more women were diagnosed with VM compared to patients with MD (p=0.001). Travel sickness was more often reported by patients with VM (pVM n=11(61%); dVM n=10 (63%)) compared to BRV (n=15 (33%); chi-square, p=0.01) and MD (n=13 (30%); chi-square, p=0.006). The percentage of patients with a positive family history of migraine was not significantly higher in VM patients compared to BRV and MD patients. Stress was reported more often to be a contributing factor for vertigo attacks for VM patients (pVM n=13 (72%); dVM n=13 (81%)) than in BRV (n=17 (38%); p=0.001). In addition, fatigue was significantly more often contributed to the vertigo complaints for VM patients compared to BRV patients (chi-square, p=0.06).

Clinical characteristics of MD

In the 43 (30%) MD patients we calculated a mean age of 53.2±14.6 and mean age of onset of 46.5±14.3 in whom 14 (35%) were women. Asymmetrical hearing loss and tinnitus were all significantly more common in patients with MD than in BRV and VM patients (all,

chi-square p=0.001). Aural fullness was more common in MD than in patients with either BRV or VM (chi-square, p=0.001). We observed that besides migraine-type headache, MD patients also suffered from migraine related symptoms such as photophobia or phonophobia.

Results of additional assessments

Results of the additional assessment are presented in **Table 3**. The median scores for hearing threshold based on PTA results by means of bone conduction thresholds were significantly higher in patients with MD than in patients with VM or BRV (Kruskal Wallis test, p=0.001 for the right ear (n=120), p=0.002 for the left ear (n=122)). None of the BRV patients reported hearing loss in association with the vertigo attacks. In 17 BRV subjects a normal hearing test result was found and in 23 (51%) hearing thresholds were symmetrically decreased based on PTA results. In the remaining five (11%) patients, PTA results were asymmetrical due to previous non-vertigo related disorders (a.o. noise induced hearing loss and trauma). In all these BRV patients, previously acquired hearing loss was accompanied by tinnitus which remained unchanged after the onset of vertigo attacks.

The median vestibular asymmetry for the caloric test was abnormal (≥ 22%) in patients with MD and scores were significantly higher in MD patients than in patients with BRV or VM (Kruskal Wallis test, p=0.001). HADS results on anxiety and depression were comparable and were found to be statistically not significant.

TABLE 3. Results of audiograms, caloric tests and HADS scores in patients with BRV, pVM, dVM and MD in median and range.

Additional assessment	BRV=45	pVM=18	dVM=16	MD=43
PTA results				
Average hearing thresholds right ear in dB (median, range)	21.5(7.0-63.0)	15.5(4.0-48.0)	17.75(4.0-25.0)	35.8(2.0-74.0)
Average hearing thresholds left ear in dB (median, range)	20.0(9.0-60.0)	17.3(5.0-45.0)	13.0(3.0-29.0)	28.5(5.0-97.0)
Caloric test results				
Vestibular preponderance (%, median, range)	11.0(1.0-87.0)	10.0(0.0-70.0)	9.0(1.0-58.0)	32.4(0.1-90.0)
HADS score				
Anxiety (median, range)	4.0(0.0-11.0)	4.5(2.0-12.0)	5.0(0.0-8.0)	4.0(0.0-13.0)
Depression (median, range)	3.0(0.0-11.0)	3.0(0.0-12.0)	3.0(0.0-11.0)	4.0(0.0-13.0)

DISCUSSION

This study aimed to investigate the clinical features of BRV, VM and MD and to assess whether clinical features could be identified that were clearly distinctive for BRV, VM or MD. In general, clinical symptoms in these three vertigo disorders were comparable and no symptom could be identified which was specifically linked to BRV. However, clinical symptoms were identified which were clearly distinctive for VM and MD.

To date, this is the first study evaluating clinical symptoms of BRV, VM and MD prospectively. In 2012, a retrospective study was published which, in line with our results, found a female predilection in BRV patients [15]. Brantberg and Baloh [16] aimed to identify symptoms that were distinctive for BRV or MD [16]. Again, a higher proportion of women were found in patients with BRV.

The mean age of onset in our study was higher than that reported by Lee *et al.* [15]. A possible explanation for this might be that patients above 64 years of age were excluded from evaluation to rule out presbyastasis. Symptoms of presbyastasis are more often accompanied by complaints of disequilibrium whereas BRV is characterised by spontaneous attacks of vertigo. As a result, we feel discrimination between BRV and presbyastasis is attainable and it is worthwhile to include patients above the age of 65.

Caloric test results based on the unilateral asymmetry percentages revealed similar median scores in patients with BRV and VM whereas scores were significantly higher in patients with MD. In line with results of previous studies [2,3,15-17] and the caloric test results it may be implied that BRV is more related to VM than to MD. However, as the etiologic concept of BRV remains unknown and the term BRV has been used in both a wider sense including varieties of migrainous vertigo, a neutral term such as BRV or recurrent vestibulopathy appears to be preferred.

With regards to patients with VM, we found that there is a clear female preponderance. This finding is in accordance with numerous previous studies which reported a female/male ratio between 1.5:1 to 5:1 [17-20].

The finding that VM patients might be more susceptible for motion sickness is supported by a recent report from Chang *et al.* [21]. They compared the prevalence of carsickness in patients with VM, MD and non-vestibular migraine. The highest percentage of lifetime carsickness was found in pVM and dVM implying this could be regarded as a clinical feature in VM. However, as definitions and methods to identify motion sickness differ across previous studies, this prevents direct comparison between studies [21,22]. In addition, it was proven that a higher rate of motion sickness is found in women [23]. Since a higher proportion of women was included in our study, the relation between motion sickness and VM may be confounded by gender. It is well known that stress can be a contributing factor for provoking attacks of vertigo in VM [24]. Even though this factor was significantly more commonly reported in VM patients compared to patients with

BRV and MD, it cannot be regarded as a distinctive clinical feature. It is also well known that stress plays a significant role in the course of MD [25,26]. It is postulated that stress activates the sympathetic nervous system leading to the release of stress hormones inducing endolymphatic hydrops [27].

With respect to the caloric test results, in conjunction with that of previous studies by Teggi *et al.* [28] and Celebisoy *et al.* [29], in 24% (n=8) of the VM patients we found a unilateral weakness based on the vestibular asymmetry (>22%). However, previous studies have found both lower and higher percentages of abnormal caloric test results [30,31]. Previous research on bithermal caloric testing in 108 healthy Spanish individuals revealed mean vestibular asymmetry of 13% in women compared to 11% in men [32]. Differences across studies may be explained by the use of different diagnostic criteria and variability in cut-off values to define caloric test abnormalities.

MD patients suffered more often from auditory symptoms compared to patients with VM or BRV. As these symptoms are mandatory for the diagnosis of MD, this is an expected finding and cannot be regarded as a distinctive clinical feature. On the other hand, a subset of the patients with MD also experienced migraine related symptoms including aura, photo- and phonophobia and a non-migraine type of headache. Similarly, previous studies have reported a higher incidence of migraine symptoms in patients with MD [33, 34]. From here it can be concluded that there is a considerable overlap of clinical symptoms especially in VM and MD which may challenge the physician in their history taking.

Caloric test results tend to be abnormal more often in patients with MD than in patients with BRV or VM. Although the caloric test is not used as a reference standard in diagnosing MD since results can be variable over time, vestibular responses tend to decrease most profoundly in the first decade [35]. Current results imply that vertigo attacks in the presence of a disputable amount of hearing loss and a profound decreased caloric responses may further the support the diagnosis of MD.

This prospective observational study suggests that due to a considerable overlap between clinical features, no symptoms could be identified which were specifically related to BRV. Nonetheless, distinctive clinical features were identified for VM and MD. Patients with VM had a clear female preponderance and a positive family history of motion sickness, although the prevalence of motion sickness may be confounded by gender. In addition, vomiting was most common in patients with MD. Even though current results do not render the differential diagnosis in BRV, the previously mentioned clinical features may assist the physician in his history taking in case VM or MD is suspected.

It is important to note that we included patients with asymmetrical hearing loss, tinnitus and aural fullness whereas Lee *et al.* [15] excluded patients with all audiological symptoms. However, in all cases the auditory symptoms existed before vertigo attacks manifested itself

due to known non-vertigo related disorders and symptoms remained unchanged after the onset of vertigo attacks.

In addition to the aforementioned remark, we were unable to subgroup data based on contributing use of medication due to the small sample sizes. Information on the vertigo attack frequency related to the type of drug use might be of clinical value. However, as several confounding factors may influence these results, e.g. spontaneous improvement, one should be cautious when proposing a causal relationship between these determinants.

In conclusion, no clinical characteristics could be identified which were distinctive for BRV. Nonetheless, we did find several distinctive clinical features for VM and MD which may assist the physician in his history taking. Prospective long-term follow-up studies in BRV would be of clinical value to determine how often BRV develops into VM or MD and study results might contribute to the discussion of whether or not BRV can be identified as a separate clinical entity.

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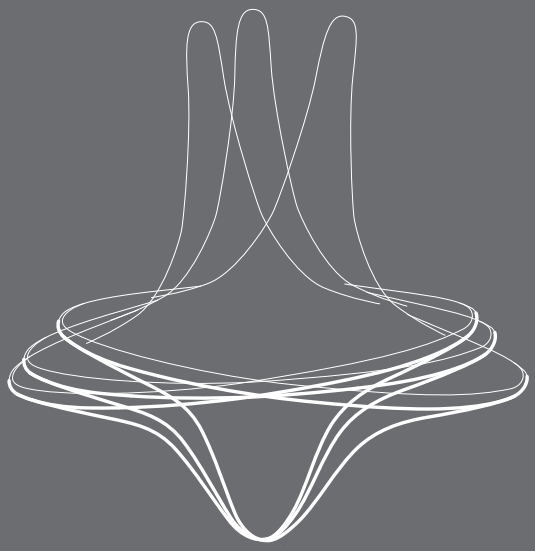
PART II

EVALUATION OF DIAGNOSTIC TESTS FOR MENIÈRE'S DISEASE



6

DETERMINING VESTIBULAR HYPOFUNCTION: START WITH THE VIDEO-HEAD IMPULSE TEST

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ABSTRACT

Caloric testing is considered the 'reference standard' in determining vestibular hypofunction. Recently, the video-head impulse test (vHIT) was introduced. In the current study we aimed to assess the diagnostic value of the vHIT as compared to caloric testing in determining vestibular function. In a cross-sectional study between May 2012 and May 2013, we prospectively analysed patients with dizziness who had completed caloric testing and the vHIT. For the left and right vestibular system we calculated the mean vHIT gain. We used a gain cut-off value of 0.8 for the vHIT and presence of correction saccades to define an abnormal vestibular-ocular reflex. An asymmetrical ocular response of 22% or more (Jongkees formula) or an irrigation response with a velocity below 15°/s was considered abnormal. We calculated sensitivity, specificity, positive and negative predictive values with 95% confidence intervals for the dichotomous vHIT. Among 325 patients (195 females (60%); aged 53 ± 17 years), 40 (12%) had an abnormal vHIT gain and 113 (35%) had an abnormal caloric test. Sensitivity was 31% (23%-40%), specificity 98% (95%-99%), positive predictive value was 88% (74%-95%), and negative predictive value 73% (67%-77%). The high positive predictive value of the vHIT indicates that an abnormal vHIT is strongly related to an abnormal caloric test result. In case of vHIT normality, additional caloric testing remains indicated and the vHIT does not replace the caloric test. In case the vHIT is abnormal, additional caloric testing is not necessary and the vHIT is useful as a first test in screening for vestibular hypofunction.

INTRODUCTION

The 'reference standard' for assessing the vestibular function is caloric testing but it uses a nonphysiological, low-frequency stimulus, is time-consuming, unpleasant and yields varying interindividual responses[1,2]. In 1988, Halmagyi and Curthoys [3] introduced a more simple, bedside method to assess vestibular function, the clinical head impulse test which had a low sensitivity, but a high specificity to detect a unilateral vestibular deficit [4,5]. Later, this test was improved by Magnusson *et al.* [6] who used video recordings of the patients' eye movements for the so-called video head impulse test (vHIT). This test measures the eye movements in response to brief, unpredictable passive head rotations (head impulses) [7]. This video-assisted procedure has been demonstrated to be a simple, valid clinical tool for testing vestibular function.

While the relationship between the clinical head impulse test and caloric testing has been investigated in several studies [4,5,8,9] , less is known about the relationship between the vHIT and caloric testing [10-12].

The goal of this study was to assess the diagnostic accuracy of the vHIT in determining vestibular hypofunction when caloric testing is considered the reference standard in dizzy patients.

MATERIALS AND METHODS

We prospectively evaluated patients with dizziness who had been referred to the Apeldoorn Dizziness Centre (ADC), a tertiary referral centre in a teaching hospital. Patients were included for analysis if caloric testing and the vHIT had been completed on the same day. After completion of the caloric test, we scheduled a break of at least 10 minutes. We assured that a nystagmus by previous caloric testing was absent and all patients had an adequate state of alertness before the start of vHIT evaluation. Patients were excluded if they had not undergone either test, if contraindications to perform caloric testing were present (e.g. tympanic membrane perforation, otitis, ear surgery) or if test results were incomplete. The diagnosis was based on a detailed clinical history, current available diagnostic standards [13-15] and/or additional diagnostic tests.

Ethical consideration

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All data was analysed anonymously.

Caloric testing

Conventional open loop bithermal caloric testing (33°C and 44°C) in both ears was used to elicit vestibular responses. The ocular response was obtained and analysed by means of a video-based system (Vestlab 7.0 ®, Otometrics, Germany). The Jongkees formula [16] was applied to express the vestibular preponderance (VP) and directional preponderance (DP) in percentages, based on the velocity of the slow phase component of nystagmus evoked by each vestibular organ. Based on the values used in previous research [4,9] and on our own experience, caloric tests were considered abnormal if the vestibular preponderance was 22% or more or the directional preponderance was 28% or more. Caloric testing was also considered abnormal if the responses for all irrigations were below normal. The criterion for bilateral weakness was a V_{max} below 15°/s for each vestibular organ (V_{max} is the sum of the slow-phase velocity for irrigation warm water + slow phase velocity for irrigation cold water).

Video head impulse test

The vHIT was measured by means of a commercially available binocular video oculography system (ICS Impulse System, version 1.20, OTOsuite Vestibular software; Otometrics, Taastrup, Denmark). The system consists of light-weight goggles with an integrated video oculography camera with sensors. An elastic band ensures fixation and minimises motion of the goggles. In a dimly lit room, subjects were instructed to maintain fixation at a dot from 1m distance. An experienced laboratory technician delivered at least 20 head impulses (10-20° angle, duration 150-200ms, peak velocity of >150°/s) in the horizontal plane with unpredictable timing and direction. The video images were analysed online by means of software which calculated Vestibular Ocular Reflex (VOR) gains. The VOR gain was defined as the ratio of the mean eye velocity (°/s) over the mean head velocity (°/s). The presence of corrective (catch-up) saccades, either overt or covert, was evaluated by the laboratory technician. To minimise biased interpretation of the vHIT test results they were evaluated by a second independent laboratory technician, who was blinded for the caloric test result. We defined a gain cut-off value of 0.8 for the vHIT, with the presence of correction saccades indicating an abnormal VOR [11,19].

Statistical analysis

The results of the study are reported according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) [4]. We calculated the mean vHIT gain for the left and right vestibular systems. We assessed whether the side of the abnormal caloric test result corresponded with the abnormal vHIT test result. Various VOR gain cut-off points have been used in previous research [11,19]. We performed a subgroup analysis considering a VOR gain of 0.6 as cut-off point for VOR dysfunction to investigate the effect on

diagnostic accuracy of the vHIT [10]. The diagnostic accuracy was evaluated by combining the caloric test and the vHIT per patient. We calculated the sensitivity, specificity, positive and negative predictive value with 95% confidence intervals (CI). The diagnostic statistical evaluation was performed with the online software from Open Source Epidemiologic Statistics for Public Health (available at http://www.openepi.com)

RESULTS

Between May 2012 and March 2013, 945 patients suffering from dizziness visited our dizziness clinic. **Figure 1** displays the test results of the 325 patients who underwent caloric testing and the vHIT. The sample population had an average age of 53 years ± 17 years and consisted of 195 females (60%). In **Table 1**, details on the diagnoses can be found. In our study population, the two most common diagnoses were hyperventilation (n=55, 17%) and benign paroxysmal positional vertigo (n=44, 14%). In 55 patients the diagnosis remained unclear despite our thorough diagnostic work-up.

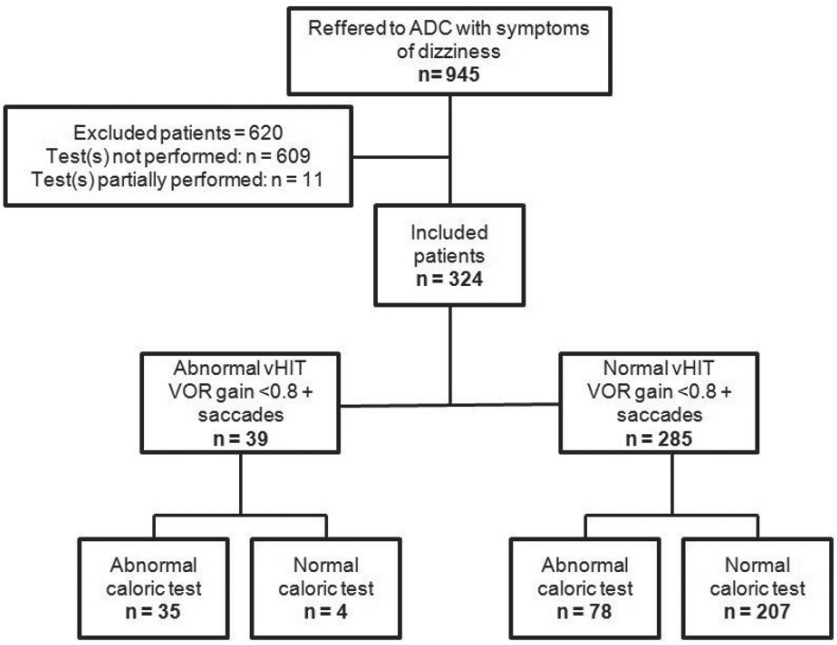

Figure 1. Flow chart for the comparison of video head impulse testing and caloric test. ADC = Apeldoorn Dizziness Centre; vHIT = video head impulse test; VOR = vestibulo-ocular reflex

TABLE 1 Diagnoses of population presenting with dizziness

Diagnosis	n (%)	Abnormal caloric test n (%)
No diagnosis	55(16.9)	8(7.1)
Hyperventilation	55(16.9)	13(11.5)
Positional vertigo	44(13.5)	11(9.7)
Somatoform/phobic	35(10.8)	8(7.1)
Menière's disease	30(9.2)	20(17.7)
Migraine	25(7.7)	6(5.3)
Vestibular neuritis/labyrinthitis	19(5.9)	18(15.9)
Unknown peripheral vestibular syndrome	16(4.9)	7(6.2)
Recurrent vestibulopathy	13(4.0)	5(4.2)
Bilateral vestibular failure	11(3.4)	10(8.8)
Orthostatic hypotension/cardiovascular	8(2.5)	2(1.7)
Central causes	8(2.5)	4(3.5)
Multisensory deficit	3(0.9)	1(0.8)
Other	3(0.9)	0(0.0)
Total	**325(100)**	**113(100)**

An abnormal caloric test was found in 113 of the 325 patients (35%). Asymmetrical responses between the left and right ear at caloric testing were found in 93 patients (29%) (mean caloric deficit 46 % ±25). In three patients the caloric test was abnormal due to abnormality of the DP. Six of these patients had a VP of 100% and thus had a unilateral vestibular paralysis. Hypofunction represented by a V_{max} below 15°/s per system was present in 58 patients (18%); in 45 patients this was unilateral, in 13 bilateral. Complete bilateral areflexia was present in five cases.

The vHIT was abnormal in 40 patients (12%). Video recordings of a normal and an abnormal video-head impulse test are shown in **Figure 2**. In one patient the side of the abnormal VOR gain did not correspond with the side of the abnormal caloric test result. In this patient a congenital (spontaneous) nystagmus reduced our ability to interpret the VOR gain, and the patient was therefore excluded from further analysis, leaving 39 patients with an abnormal vHIT. All but six patients with a VOR gain below 0.8 had either covert or overt saccades. **Figure 3** displays the mean canal paresis deficit as a function of the normal and abnormal vHIT results. Patients with an abnormal vHIT had a significantly higher mean caloric deficit than patients with a normal vHIT (mean difference 30%, 95%CI:18%-42%, $p<0.001$). All patients with a gain below 0.6 had corrective saccades. No adverse events occurred while performing any of the tests.

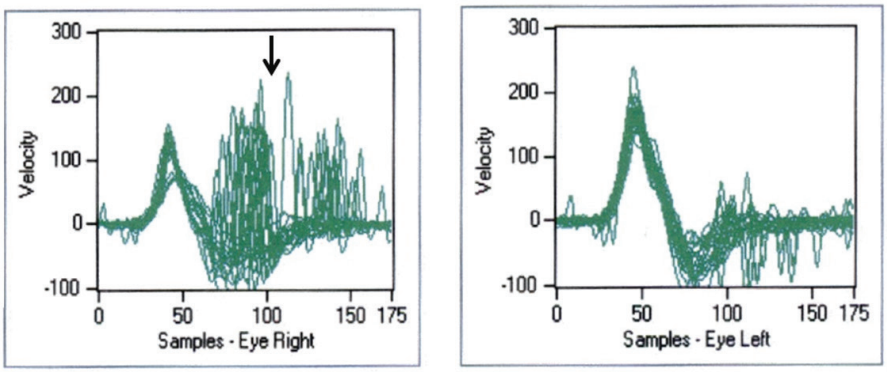

Figure 2. A pathological (eye right) and an unremarkable (left eye) vHIT are shown. In the right eye, the eye velocity is lower including the presence of (overt) correction saccades (*arrow*)

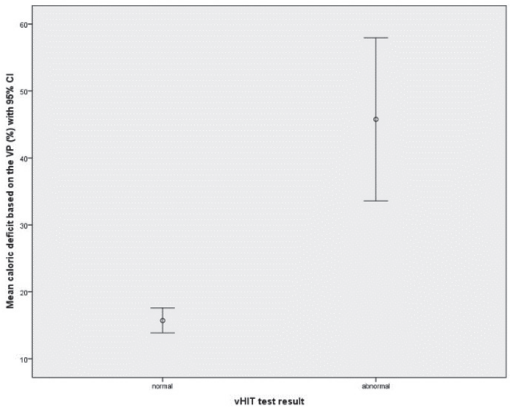

Figure 3. Mean canal paresis deficit as a function of the vHIT test result. Data represent mean and corresponding 95% confidence intervals.

In comparison with caloric testing the vHIT (with a VOR gain < 0.8 and corrective saccades) had a sensitivity of 31% (95% CI: 23%-40%), a specificity of 98% (95% CI: 95%-99%), a positive predictive value (PPV) of 90% (95% CI: 76-96) and a negative predictive value (NPV) of 75% (95% CI: 70-79) (**Table 2a**).

Subanalysis, using a VOR gain of 0.6 as cut-off point for vestibular dysfunction, resulted in 25 patients (7.7%) with an abnormal vHIT (**Table 2b**). Caloric test results were abnormal in all these subjects. The subanalysis on diagnostic accuracy resulted in a sensitivity of 22% (95% CI: 16%-31%), a specificity of 100% (95% CI: 98%-100%), a PPV of 100% (95% CI: 87%-100%), and a NPV of 71% (95% CI: 65%-76%).

TABLE 2a Results of the vHIT and caloric testing with a VOR gain cut-off value of <0.8

	Caloric test*		
vHIT	Abnormal (n)	Normal (n)	Total
Abnormal (n)	35	4	39
Normal per system(n)	78	207	285
	113	211	324
Sensitivity was 31% (95% CI: 23%-40%), specificity 98% (95% CI: 95-99), positive predictive value (PPV) 90% (95% CI: 76-96), negative predictive value (NPV) 75% (95% CI: 70-79)			

*Cut-off values for an abnormal caloric test were a VP ≥ 22%, a DP ≥ 28% and/or a V_{max} < 15°/s per vestibular system.

TABLE 2b Results of the vHIT and caloric testing with a VOR gain cut-off value of <0.6

	Caloric test*		
vHIT	Abnormal (n)	Normal (n)	Total
Abnormal (n)	25	0	25
Normal per system(n)	88	211	299
	113	211	324
Sensitivity was 22% (95% CI: 16%-31%), a specificity was 100% (95% CI: 98%-100%), a PPV of 100% (95% CI: 87%-100%), and a NPV of 71% (95% CI: 65%-76%).			

*Cut-off values for an abnormal caloric test were a VP ≥ 22%, a DP ≥ 28% and/or a V_{max} < 15°/s per vestibular system.

DISCUSSION

Synopsis of key findings

We aimed to assess the diagnostic value of the vHIT compared to caloric testing in determining vestibular function in patients suffering from dizziness. In a large prospective cohort of 325 patients, we found a sensitivity of 31% and a specificity of 98%, a PPV of 90% and a NPV of 75% for the vHIT when compared to caloric testing. In the subgroup analysis, using a VOR gain of 0.6 as cut-off point, the sensitivity decreased to 22%, the specificity and the PPV reached 100% and the NPV decreased to 71%.

Comparison with other studies

Whilst the specificity we found is in line with previous studies, we report a lower sensitivity. Previous studies evaluating the vHIT compared to caloric testing reported specificities between 92% and 100% but sensitivities between 41% and 78% [10-12]. None of these studies reported the predictive values (PPV and NPV) of the vHIT [10-12].

The differences in sensitivities may be explained by the fact that these studies evaluated the diagnostic value of the vHIT in much smaller groups than our study [10-12]. Besides, analyses were performed on retrospectively collected data [10,11] and they used different cut-off values defining abnormal vHIT gain and caloric test results [10-12].
The highest sensitivity of 78% was found by McCaslin *et al.*[12], who analysed 115 patients under the age of 65. A possible explanation for the higher sensitivity may be that the mean caloric deficit values were higher in McCaslin's study population than in ours [12] as the sensitivity of the vHIT depends on the canal paresis factor. For instance, Bartolomeo *et al.*[10] reported a sensitivity of 100% when the caloric vestibular deficit limit value was set to 62.5% or higher. In our population a mean caloric deficit of 46 ±25% was found. Mahringer and Rambold [11] reported a mean caloric deficit of 48±18%. In this study, 71 of the 172 patients were identified with an abnormal vHIT which is comparable to our results. The mean caloric deficit in the population studied by Bartelomeo *et al.*[10] was 78.7±21.2% which explains why in all patients the vHIT was abnormal. McCaslin *et al.*[12] did not provide information on mean caloric deficits. Therefore, it is not clear whether the data are comparable to caloric deficits in our population.

Strengths of the study

Prior studies [10-12] evaluating the diagnostic accuracy of the vHIT did not include the caloric response per se when defining an abnormal test result in patients with symmetrical or non-pathological asymmetrical caloric test responses. They focused on those patients who had a unilateral caloric weakness as calculated by the Jongkees formula [16]. By including patients with a low caloric response per se, represented as a V_{max} below 15°/s per vestibular system, we identified 20 additional patients with vestibular hypofunction. Ten of these patients had a decreased VOR gain based on the vHIT, which implies that it is relevant to include these patients in a diagnostic study. Another important finding was that a vHIT gain cut-off value of 0.6 was clinically useful as a PPV of 100% was reached [10]. An abnormal vHIT using this cut-off value strongly indicates a severe or total canal paresis and excluded patients with a borderline vHIT test result.

Clinical applicability of the study

A practical implication of the present study is that the vHIT may be used as a first diagnostic test in determining vestibular hypofunction. An abnormal vHIT is related to significant canal paresis especially when the gain is less than 0.6, and therefore additional caloric testing is not necessary. The advantage of using the vHIT is that it is a simple, safe and non-invasive test that allows repeated testing within a few minutes. Drawbacks of caloric testing are that results may be influenced by skull characteristics, temporal bone circulation, alertness of the patient and previously administered medication [18,19].

The use of the vHIT as a screening tool for vestibular hypofunction is supported by the economic evaluation performed by Rambold *et al.* [20]. This study assessed the optimal diagnostic sequence for the vHIT and the caloric test expressed as the shortest diagnostic time. The diagnostic time was significantly shortened when the vHIT was performed first, even if additional caloric testing was necessary in case of a normal vHIT test result. Based on the time saving aspect it was concluded that starting with the vHIT was the most optimal diagnostic sequence for economic reasons.

Limitations of the study

It is important to bear in mind that several factors may have influenced study results. First, due to differences in their diagnostic characteristics, the different test results of the vHIT and caloric testing provide unique information regarding the integrity of the horizontal semicircular canals. Evaluation by means of the vHIT involves a high frequency range (up to 5 Hz), whereas the caloric test reflects a low frequency range (approximately 0.003 Hz). The vHIT causes a physiological endolymphatic flow, whereas caloric testing involves a non-physiological non-gravity dependent stimulus. The tests provide complementary information about the horizontal semicircular canals and should be used adjunct to one another. It remains unknown to which extent dissociation of vHIT and caloric testing can be explained by these differences.

Secondly, the diagnostic work-up was performed by multiple, yet experienced, laboratory technicians. Although the vHIT is considered a relatively objective diagnostic method, as VOR gains are calculated by software, lab employees may judge the presence of correction saccades differently.

Thirdly, the clinical meaning of the DP is controversial and does not always correlate with peripheral vestibular disorders [18]. As abnormality of the DP led to an abnormal caloric test result in only three cases little importance should be given to the DP when interpreting caloric test abnormalities in our study.

Lastly, as only 34% of all 925 consecutive test patients could be included for further analysis, selection bias may have influenced our test results. However, all patients who visited our clinic were eligible for inclusion without applying pre-selection based on caloric test abnormalities. Therefore, we believe the low percentage of included patients does not inhibit applicability of our study findings.

CONCLUSIONS

In conclusion, comparison with caloric testing revealed that the vHIT is a very specific rather than sensitive test for detecting vestibular hypofunction. In case of a normal vHIT, additional caloric testing remains indicated and the vHIT does not replace the caloric test.

The high positive predictive value of the vHIT, especially if a gain cut-off point of 0.6 is applied, indicates that an abnormal vHIT is strongly related to an abnormal caloric test result. Therefore, in case of an abnormal vHIT, additional caloric testing is not necessary. We conclude that the vHIT is clinically useful as a first test in determining vestibular hypofunction in dizzy patients.

Competing interests: The authors declare that they have no conflict of interest.

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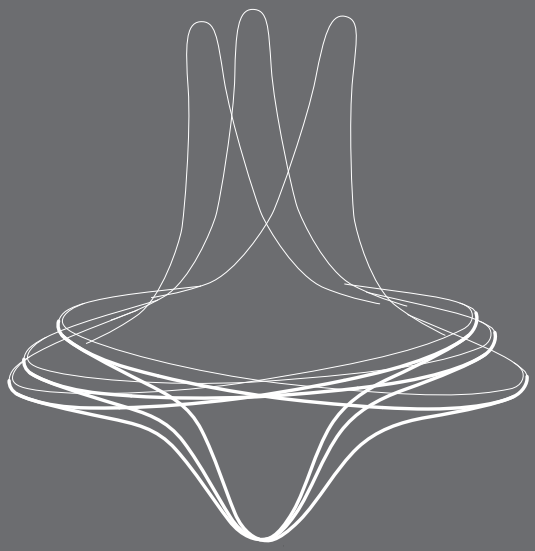

7

VIDEO-HEAD IMPULSE TEST RESULTS IN PATIENTS WITH MENIÈRE'S DISEASE RELATED TO DURATION AND STAGE OF DISEASE

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ABSTRACT

Background: The video-head impulse test employs the vestibulo-ocular reflex (VOR) to assess vestibular function. To this day, no consensus has been reached among scientists in terms of whether or not vHIT results change in MD patients as the disease progresses.

Objective: To assess whether the vHIT is more often abnormal in later stages of MD compared to earlier stages.

Methods: We retrospectively analysed patients with 'definite' MD who had undergone a vHIT and caloric test between 2012 and 2015. Patients were evaluated based on duration of disease in years (≤1, >1≤5, >5≤10, >10) and stage of disease (stage I and II versus III and IV). For the vHIT, an abnormal vestibulo-ocular reflex was defined as a gain cut-off value of ≤0.8 and presence of correction saccades including subanalyses using a cut-off value of ≤0.9.

Results: In 89 definite MD patients (42 (47%) male, mean age 55±5 (SD)), data on both the caloric test and the vHIT were available. The risk of an abnormal vHIT was 25% in patients with a duration of disease over 10 years compared to 22% in the patients with a disease duration of 10 years or less (risk difference 3%, 95% CI:-28% to 35%), p=0.82). The risk for an abnormal vHIT in the Stage I and Stage II was 17% compared to 26% in Stage III and IV (risk difference 9%, 95% CI:-30% to 11%). When using a cut-off value of 0.9 we also did not demonstrate a relationship between the duration of disease and the proportion of abnormal vHIT test results.

Conclusions: There is no relationship between the proportion of abnormal vHIT test results in patients with MD and either duration or stage of disease.

INTRODUCTION

Menière's disease (MD) lacks a diagnostic reference standard to objectify the diagnosis. The diagnosis of MD is based upon its clinical characteristics accompanied by documented hearing loss [1] rather than the use of vestibular tests. Although the caloric test may be considered as the reference standard for assessing vestibular function, great variability in the results is found in MD, making the test unsuitable to serve as a reference standard [2-4]. In the pursuit of objectifying MD, scientific studies combined results of vestibular tests such as the caloric test and the recently developed video-head impulse test (vHIT) [5,6]. Although both the caloric test and the vHIT measure vestibular function, they capture distinct phenomena [7,8]. While the caloric test uses a non-physiological low-frequency stimulus, the vHIT measures head and eye movements during physiological high-velocity rotatory head thrusts [9-11].

Based on previous research in patients with MD we know that caloric test responses decrease most profoundly in the first decade after which responses stabilize at a fixed level of hypofunction of approximately 50% [12-14]. Similarly, to that of caloric testing, one would expect that abnormal vHIT results are more common in MD in the chronic stage. Maire and van Melle [15] found that in the chronic phase of the disease (>12 months), the VOR gain decreased, resulting in an abnormal vHIT result. One may argue whether the chronic stage begins after one year of vertigo symptoms since the total duration of disease is estimated to last 20 years [16]. On the other hand, Cerchiai *et al.* [17] found that the proportion of abnormal vHIT results was similar in patients with 'early' MD (5 years or less) compared to those with 'late' MD (more than 5 years).

Based on the disagreement between pervious study results, we aim to evaluate whether the vHIT is more often abnormal in patient with a later stage of disease than in those with an early stage, related to either duration of vertigo attacks in years or level of hearing loss. In case progression of disease is consistently related to an increase of abnormal vHIT results, this may serve as a diagnostic hallmark in the course of the disease.

MATERIALS AND METHODS

In this study, we retrospectively evaluated patients diagnosed with MD who visited a tertiary dizziness clinic from 2012 to 2015 (n=343). Patients were included if they met the criteria for 'definite' MD as defined by the AAO-HNS in 1995 [1] (n=250). No patients with 'certain' MD were included as we did not seek histopathological confirmation in patients with 'definite' MD. A single attack of vertigo accompanied by unilateral hearing loss was regarded to be clinically more compatible with (viral) labyrinthitis, therefore patients matching the criteria of 'probable' MD were not included in this analysis either. We excluded 'possible' MD as it represents a less well defined clinical entity and this population

may contain vertigo related diseases as well (e.g. vestibular migraine) [18]. We categorized patients according to the duration of disease based on the duration of symptoms in years. In addition, the stage of the disease was based on the four-tone average of the pure-tone thresholds at the frequency of 0.5, 1, 2 and 3 kHz of the worst audiogram in accordance with the AAO-HNS 1995 guideline [1]. Stage I was defined as a four-tone average (rounded to the nearest whole number) of 25 decibel (dB) or less. Stage II represented an average hearing loss of 26 to 40 whereas patients with a Stage III suffer from an average hearing loss between 41 to 70 dB. Stage IV included patients with an average hearing loss of more than 70 dB. All data were analysed anonymously and procedures were performed in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments.

vHIT testing

The vHIT was measured by means of a commercially available mono-ocular video oculography system (ICS Impulse System, version 1.20, OTOsuite Vestibular software; Otometrics, Taastrup, Denmark). The system consists of light-weight goggles with an integrated video oculography camera with sensors. An elastic band ensures fixation and minimises motion of the goggles. In a well-lit room, subjects were instructed to maintain fixation at a dot from 1 m distance. An experienced laboratory technician delivered at least 20 head impulses per side (10-20° angle, duration 150-200ms, peak velocity of >150°/s) in the horizontal plane with unpredictable timing and direction [19]. The VOR gain was defined as the ratio of the eye velocity (°/s) over the head velocity (°/s). The presence of refixation (catch-up) saccades, either overt or covert, was evaluated by the laboratory technician. In line with previous literature, vHIT testing was considered to be abnormal if VOR gain was <0.8 in the presence of refixation saccades [5]. The standard ICS Impulse system was used to calculate gain values, which computed the area gain over the whole interval. In other words, gain values were calculated on the area of the head and eye velocity sample resulting from the head impulse, which was then divided to produce the gain value (position gain). This in contrast to systems in which the gain is based on a fixed interval length in milliseconds in which at a local point the gain is calculated (velocity gain). Based on previous research, higher gain values where found in the ICS Impulse system, as a result of which it is suggested to use a higher cut-off point. Therefore, an additional analysis was performed using a cut-off value of 0.9 [20,21].

Caloric Testing

Bithermal caloric testing was performed using an open loop water irrigation system. Similar to the vHIT methods, details have been described earlier [19]. Asymmetry of the vestibular function, expressed as the vestibular preponderance (VP) and the directional

preponderance (DP), was calculated by means of the Jongkees' formula [22]. Based on the values used in previous research [23, 24] and on our own experience, caloric tests were considered abnormal if the vestibular preponderance was 22% or more or the directional preponderance was 28% or more. Caloric testing was also considered abnormal if the irrigation response had a Vmax below 15°/s (bilateral vestibular hypofunction) per vestibular organ for both ears.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) (Version 18) was utilized for statistical evaluation in this study. We calculated frequencies for sex and type of MD, uni- or bilateral involvement, vestibular hypofunction and the duration and stage of the disease in our population. Means and standard deviation were calculated for age and the vHIT gain for both the left and right vestibular system. Moreover, we compared the vHIT gain per ear for the side of the reduced caloric response versus the side of the normal caloric response. Differences between acute versus chronic and stage I and II versus III and IV with respect to normal and abnormal vHIT result were assessed by means of cross-tabulation and analysed using the Chi-square test. A p-value of less than 0.05 was considered significant.

RESULTS

Within the MD population, data with regards to the vHIT and the caloric test was available in 89 (36%) patients. Patients had a mean age of 55±5 years and 42 (47%) were male. We found that 84 (94%) suffered from symptoms of unilateral MD and 5 (6%) had symptoms of bilateral MD. The mean duration of disease was 5±6.2 years. The mean vHIT gain on the left side was 0.91±0.14 and 0.99±0.2 on the right side. Based on the level of hearing loss, 3 (3%) patients met the criteria for Stage I. Fifteen (17%) patients could be classified as stage II, whereas Stage III and Stage IV comprised 56 (63%) and 13 (15%) of the patients respectively. In two patients no information on the amount of hearing loss was available. **Table 1** shows the percentage of abnormal caloric tests and VHIT test results related to stage of disease. A progressive increase in the number of patients with an abnormal caloric test was seen when results were related to stage of the disease. Results of the per ear analyses are shown in **Figure 1.** In 85% of the ears a unilateral vestibular hypofunction or bilateral hypofunction was identified by the caloric test. We found that in 10% of the ears, both the vHIT test and the caloric test identified an ipsilesional vestibular hypofunction.

TABLE 1. Results in MD patients who underwent both the caloric and vHIT test (n=89) with a cut-off value of 0.8 related to stage of disease.

	Percentage (number/total)			
	Stage I	**Stage II**	**Stage III**	**Stage IV**
Abnormal caloric test results	33 (1/3)	47 (7/15)	79 (44/56)	92 (12/13)
Abnormal vHIT results	0 (0/3)	20 (3/15)	23 (13/56)	38 (5/13)

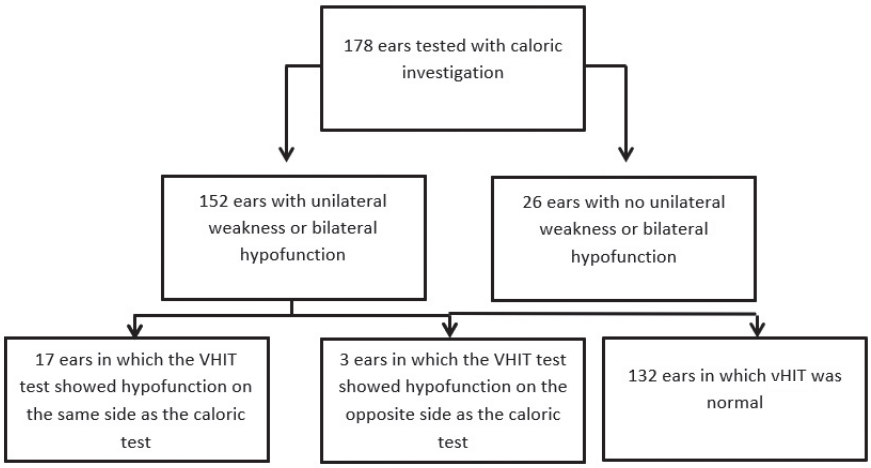

Figure 1. Results per ear regarding ipsilesional and contralesion vHIT test results based on a unilateral caloric weakness or bilateral hypofunction.

vHIT test results related to the duration and stage of disease

Table 2a illustrates the proportion of abnormal vHIT test results in MD related to the duration of disease in years (less than 1 year, from 1 year to 5 years, less than 5 years, from 5 years to 10 years, more than 10 years) and stage of disease (stage I to IV). The absolute risk for an abnormal vHIT was 22% in the group with a disease duration of less than one year compared to 22% in the group with a disease duration over one year (risk difference 0.4%, 95% CI: -19% to 20%), p=0.96). The absolute risk for an abnormal vHIT was 22% for patients with a duration of disease of >1 year to 5 years and > 5 years to 10 years. This risk was comparable (21-23%) to patients with a disease duration in the remaining time interval. The absolute risk was 25% in patients with a duration of disease over 10 years compared to 22% in the patients with a disease duration of 10 years or less (risk difference 3%, 95% CI: -28% to 35%), p=0.82). The absolute risk for an abnormal vHIT in the Stage I and Stage II was 17% compared to 26% in Stage III and IV (risk difference 9%, 95%

CI: -30% to 11%), p=0.41). The absolute risk for an abnormal vHIT was 0% for Stage I compared to Stage III and IV 6% (risk difference 6%, 95% CI: -12% to 1%, Fischer Exact test p=0.8). Based on the per ear analyses of the proportion of abnormal vHIT test results we did not find significant differences between groups based on the duration of disease.

TABLE 2a. Results of the vHIT related to the duration and stage of disease using a cut-off value of 0.8

	Abnormal vHIT n (%)	**Total**
≤1 year	6 (22)	27
>1≤5 years	5 (21)	24
>5≤10 years	5 (22)	23
>10 years	2 (25)	8
Stage I	0 (0)	3
Stage II	3 (20)	15
Stage III	13 (23)	56
Stage IV	5 (38)	13

No significant difference in the proportion of patients with an abnormal vHIT was found when MD patients with a duration of disease of ≤1 year were compared to MD patients with a duration of disease of >1 years (chi-square p=0.9). This was similar after comparing patients with disease duration of ≤10 years to patients with a disease duration >10 years (chi-square p=0.8). No significant difference on the proportion of patients with an abnormal vHIT was found when MD patients with a Stage I or II were compared to patients with a Stage III or IV (chi-square Stage I, II versus Stage III/IV p=0.41)

vHIT test results related to the duration and stage of disease using a cut-off value of 0.9

Like the previous analyses, the proportion of abnormal vHIT test results were calculated based on the duration and stage of the disease as shown in **Table 2b**. The absolute risk for an abnormal vHIT was 63% in the group with a disease duration of less than one year compared to 56% in the group with a disease duration over one year (risk difference 7%, 95% CI: -16% to 29%), p=0.29). Absolute risks for an abnormal vHIT for patients with a duration of disease of >1 year to 5 years and >5 years to years were 67% and 48 % respectively. Risks in patients in the remaining time intervals were 55% and 62% resulting in risk differences of 11% (95% CI: -11.3%-34.3%, p=0.17) and -15% (95% CI: -39%-9%, p=0.1). The absolute risk was 50% in patients with a duration of disease over 10 years compared to 60% in the patients with a disease duration of 10 years or less (risk difference -9.5%, 95% CI: -46% to 27%), p=0.3). The absolute risk for an abnormal vHIT in the Stage

I and Stage II was 67% compared to 55% in Stage III and IV (risk difference 12%, 95% CI: -13% to 36%), Fischer Exact test p=0.27). The absolute risk for an abnormal vHIT was 33% for Stage I compared to Stage III and IV 58% (risk difference -25%, 95% CI: -79% to 29%, Fischer Exact test p=0.39).

TABLE 2b. Results of the vHIT related to the duration and stage of disease using a cut-off value of 0.9

	Abnormal vHIT n (%)	**Total n**
≤1 year	17(63)	27
>1≤5 years	16(67)	24
>5≤10 years	11(48)	23
>10 years	4(50)	8
Stage I	1(33)	3
Stage II	11(73)	15
Stage III	29(52)	56
Stage IV	9(69)	13

No significant difference in the proportion of patients with an abnormal vHIT was found when MD patients with a duration of disease of ≤1 year were compared to MD patients with a duration of disease of >1 years (chi-square p=0.3). This was similar after comparing patients with disease duration of ≤10 years to patients with a disease duration >10 years (chi-square p=0.3). No significant difference on the proportion of patients with an abnormal vHIT was found when MD patients with a Stage I or II were compared to patients with a Stage III or IV (chi-square Stage I, II versus Stage III/IV p=0.38)

DISCUSSION

Previous research has shown that caloric test responses in patients with MD tend to decrease in the first decade of disease [11-13]. Like that of the caloric test, one would expect abnormal vHIT results to be more common in MD patients who are in a later stage of the disease. We evaluated whether vHIT abnormality is more common in patients who are in a later stage of the disease as opposed to those in an earlier stage.

The vHIT was related to the duration of symptoms in years and the stage of disease. No changes in the proportion of abnormal vHIT results were found when related to progression of disease.

A recent retrospective chart review by Cerchiai *et al.* [16], evaluated vHIT findings of 'definite' MD patients who were treated with either intratympanic gentamicin or conservatively (dietary modifications combined with acetazolamide, hydrochlorothiazide

or betahistine) and related results to duration of disease. In line with our study findings, no relation was found between the VOR gain results and the duration of disease.
Zulueta-Santos *et al.* [25] evaluated the distribution of normal and abnormal vHIT results in all planes (i.e. evaluation of horizontal, superior and posterior canals) in 36 patients with definite unilateral MD. A rather diverse set of results was found for the affected and unaffected ear. They did not find a relation between the degree of canal function loss expressed by the vHIT and the duration of disease or hearing loss.
However, Maire *et al.* [14] concluded that the stage of the disease could affect the vHIT test result. They stated that in early Menière's disease, the VOR gain is higher towards the affected side as opposed to the intact side, while the opposite is seen in patients in a later stage of the disease. Funabiki *et al.* [26] used the direction of nystagmus attempting to explain this dynamic change in the peripheral vestibular system. They stated that VOR gain was higher towards the affected side when an ipsilateral nystagmus was present and decreased when there was a contralateral nystagmus. Subsequently, Odawa *et al.* [27] found that just prior to vertiginous periods the VOR gain was higher in the direction of the ear with MD versus the contralateral unaffected ear.
The dissociation between the vHIT and the caloric test may be explained by damage primarily to the low-frequency spectrum in the vestibular apparatus in Meniere's disease. The caloric response represents a low frequency (0.002-0.004 Hz) rotation, whereas the vHIT response involves a more physiological, high frequency rotation, representing a frequency up to 5 Hz [9,10].
Moreover, various studies on the vHIT have used different techniques to calculate the gain. One common method is the local sample point to point gain in which the velocity gain is calculated from a fixed interval length 60 milliseconds after the head impulses is started [5]. In our study the gain was calculated from the area of the head and eye velocity over the responses after which it was divided to yield the gain. Based on previous research on this matter, standard higher gains were found using this method from which it was recommended to use higher cut-off values [19,20].
With respect to caloric test responses and vestibular hypofunction, previous studies showed variability in cut-off values. A recent consensus document published by Strupp *et al.* [28] used V_{max} cut-off values of less than 6 degrees per second to define vestibular hypofunction whereas a cut-off value of 35 degrees per second is used by the University Medical Centre in Maastricht. We used a relatively low cut-off value of 15 degrees per second to identify patients with a vestibular hypofunction, when comparing it to the cut-off values defined by the University Medical Centre Maastricht. A lower cut-off value results in a larger group of patients with a false positive result. In clinical practice we prefer to include patients with false positive results to minimize the proportion of false negative results, as a smaller group of patients will be deprived of further diagnostic evaluation [30].

It is proposed that different nerve fibers in the crista ampullaris are stimulated depending on the velocity of the head-movement [30]. Caloric testing would stimulate the regular afferent from the peripheral zones whereas high-velocity head movements during the vHIT are believed to stimulate irregular centrally located afferents [10]. Based on histopathological research it is suggested that MD mainly affects the peripheral zones and therefore leads to abnormality of the caloric test [7]. As the disease progresses, central damage to the crista will then cause abnormality of the VOR responses. Although the theory seems plausible, our study demonstrated various responses of normal and abnormal vHIT results in patients with both recent onset of symptoms and those with progressed disease.

To date, this is the largest study analysing vHIT characteristics in patients with MD. Moreover, this is the first study quantifying normal and abnormal vHIT test results related to the duration and the stage of disease. Another strength of this study was the use of AAO-HNS 1995 guidelines by which our MD population was defined and staged in a standardized way.

However, there are some limitations which need to be considered when interpreting our study findings.

First, analysis could only be performed in 89 out of 250 patients (36%) due to the absence of information on both the caloric test results and the vHIT results for the remainder of the population. Therefore, selection bias may have influenced the results.

Mainly, the reduction of the sample size is based on a practical limitation. While two caloric systems were available for caloric testing, only one test system was accessible at the department for the vHIT. The reduced number in vHIT results can be considered as random missing information as no pre-selection criteria on patients were applied before performing the diagnostic tests. Therefore, it is unlikely that the results of our study are clinically not applicable.

Secondly, both tests have been evaluated in a retrospective way, between vertigo spells and without serial evaluation. A recent retrospective case series by Lee *et al.* [31] analysed results of both tests during vertigo attacks in patients with MD at various stages of the disease. They concluded that vHIT results tend to fluctuate when tested during the irritative (vertigo) phase compared to the paretic phase. To fortify information on the canal function based on vHIT test results in MD, serial evaluation of individuals may provide relevant information with respect to changes of results over time.

Thirdly, only vHIT results for the horizontal canal were analysed whereas the vertical and lateral semicircular canals may also be of importance as the whole membranous labyrinth is believed to be affected in MD. It is possible that vertical and lateral semicircular canals are differently affected by the disease and may be able to show a consistent change in vHIT results when related to disease progression.

Lastly, eight patients were treated with intratympanic injections whereas the remaining received conservative treatment (medication, Prisma® glasses). Due to the vestibulotoxic effect of gentamicin, abnormality of the vHIT is expected in all these patients. In six of these patients, information on the age of onset was available. Subanalysis revealed that these patients had varying disease duration and both normal and abnormal vHIT results were found. However, the small sample size of patients analysed in the intratympanic group should be considered when interpreting these findings.
We retrospectively analysed vHIT test results related to the stage and duration of disease, and found no relation between the two. Future, prospective, serial evaluation of individuals analysing all semicircular canals may be able to provide information on consistent changes of the vHIT and may serve as an objective finding in the diagnostic process in MD.

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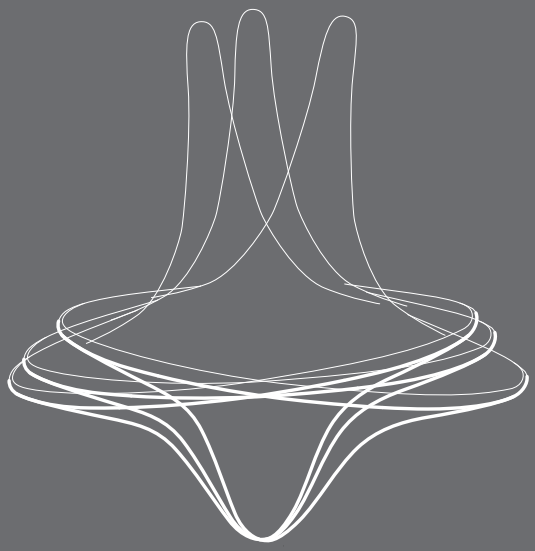
PART III

EVALUATION OF INTERVENTONS FOR MENIÈRE'S DISEASE



8

THE EFFECT OF VESTIBULAR REHABILATION IN PATIENTS WITH MENIÈRE'S DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To systematically review the evidence on the effect of vestibular rehabilitation in patients with Menière's disease (MD) on balance and dizziness-related quality of life.

Data sources: A literature search was conducted in the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Web of Science and CINAHL databases.

Review methods: Articles were reviewed by two independent authors and data were compiled in tables for analysis regarding balance (i.e. posturography) and dizziness-specific quality of life in patients with MD. A comprehensive search was performed up to November 2015. Studies on relevance and methodological quality were assessed by means of the Cochrane Risk of Bias tool. For outcome on balance and quality of life we calculated mean differences and their 95% confidence intervals (CIs).

Results: A total of 986 unique papers were retrieved. Five studies, including a total of 498 patients, fulfilled the eligibility criteria including two randomised controlled trials and three prospective cohort studies. There was no study with a low risk of bias. We found inconsistent evidence for the effect of vestibular rehabilitation on balance and dizziness-related quality of life.

Conclusion: Based on the low quality of the selected studies, it is inconclusive whether there is a positive effect of vestibular rehabilitation in patients suffering from Menière's disease on balance and dizziness-related quality of life.

Keywords: Menière's disease, physiotherapy, vestibular rehabilitation, vertigo

INTRODUCTION

Ménière's disease (MD) is an inner ear disorder characterized by spontaneous attacks of vertigo, fluctuating hearing loss, tinnitus, and/or aural fullness [1]. According to the guidelines of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [2], "definite" MD patients have experienced at least two episodes of vertigo lasting at least 20 minutes, they suffer from a hearing loss of 20 decibels or more and have tinnitus or aural fullness in the affected ear.

The precise etiology is unknown and therefore a clear treatment strategy is still missing [3,4]. Many treatment options have been studied for this disease, primarily aiming to reduce or control vertigo attacks and to preserve hearing [5-7]. In the course of the disease vertigo attacks may lead to the loss of vestibular function causing balance problems [8]. Unfortunately, little attention has been directed at reducing balance or unsteadiness complaints associated with MD.

There has been increasing interest in the value of exercises for patients with balance problems, known as vestibular rehabilitation (VR) [9]. VR includes Brandt-Daroff exercises, Cawthorne-Cooksey exercises, viewing exercises and balance exercises. All these exercises include head and trunk movements to stimulate the vestibular system. The aim of these exercises is to improve the visual-vestibular interaction and to increase the static and the dynamic postural stability. They can have a positive effect on the quality of life by reducing symptoms of dizziness and anxiety [10]. The clinical recovery is thought to rely on the following mechanisms: compensation/ habituation, which is a central process and refers to the reduction in symptoms produced by specific movements and occurs through repetitive exposure to the movement; adaptation, which is the recovery of the dynamic vestibulo-ocular responses due to the ability of the vestibular system to make long-term changes in the neuronal response to input; and substitution, which is the use of other strategies to replace the lost function [11]. In 2011 a Cochrane review assessed the effect of VR for peripheral vestibular hypofunction [12]. The review concluded that VR had an overall positive effect on balance and disequilibrium complaints.

While the efficacy of VR has been evaluated in several vestibular diseases, no systematic review has been conducted yet to search for and appraise the evidence for MD. Therefore, we aim to review current literature on the effect of VR on balance and dizziness-related quality of life in patients suffering from MD.

METHODS

A literature search was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Search and selection

A systematic literature search was conducted to investigate the effect of VR on balance problems and dizziness-related quality of life in patients with MD. According to the guidelines set forth by the Institutional Review Board of Gelre Apeldoorn, Apeldoorn, The Netherlands, this study met the criteria for nonhuman subject research, and as a result board approval was not required. A search of the following EMB databases was performed: the Cochrane Library, MEDLINE (PubMed), Embase, Web of Science and CINAHL. Databases were searched using the following keywords: "Menière's disease", "endolymphatic hydrops" and "vestibular rehabilitation","physical therapy" and "exercise" (see Appendix 1) from inception to November 2015. Two independent authors (B.E. and E.H.) excluded duplicates and screened titles and abstracts for eligibility of inclusion. Papers were included if the VR included Brandt-Daroff exercises, habituation exercises, balance exercises or self-treatment. We excluded interventions which assessed the effect of electrophysiological or pharmacological management. A combination of VR exercises with pharmacological management was allowed. We excluded systematic reviews, opinion papers, animal studies, and case reports comprising 10 patients or less (see Figure 1 for in- and exclusion criteria). No restrictions on language, publication year or publication status were applied.

Two independent reviewers (B.E. and E.H.) screened full texts of eligible articles. We independently extracted data from the included studies regarding study design, sample size, age, sex, type and frequency of VR exercises, the outcomes of intervention and follow-up. If the full text was unavailable and/or study characteristics remained unclear after full text screening, authors were contacted by email. Reference lists from identified studies were examined to find further potentially eligible papers. Selection was based on full consensus of both reviewers.

Data collection and analysis

Two authors (B.E. and E.H.) independently extracted descriptive data on patient population, type of intervention and outcomes. The outcome measures included the results on balance (e.g. posturography) and dizziness-specific quality of life.

Records were assessed on relevance and validity by two independent authors (B.E. and E.H.) using predefined criteria. Relevance involved the applicability of the study adequately answering the research objective providing information on (1) the MD patients, (2) the VR program, and (3) the outcomes. Study items were classified as either 'satisfactory' (●) or 'unsatisfactory' (○). Whenever an item was not reported, it was rated as "unclear" (?).

Evaluation of the validity was done by means of the 'risk of bias tool' as published by the Cochrane Collaboration.[14] Randomised controlled trials (RCTs) and cohort studies were evaluated separately. In the evaluation of cohort studies, we excluded evaluation on random

sequence generation (1), allocation concealment (2) and methods of blinding (participants (3) and outcomes (4)). Both RCTs and cohort studies were evaluated on the selection of patients (5), the standardization of the intervention (6) and outcome assessment (7), the incompleteness of data (8) and selective reporting (9). If there was any disagreement on inclusion or exclusion, this was settled by discussion, if necessary in the presence of a third reviewer (H.v.d.Z., T.B. and/or P.B.). If the studies met all these criteria, they were classified as having a high validity (i.e. low risk of bias).

We checked the studies included for methodological and statistical heterogeneity. If the data were sufficiently homogenous, we pooled outcome data. Statistical heterogeneity was quantified by the I^2 statistic. An I^2 value greater than 50% was considered to indicate substantial heterogeneity (Handbook 2011, The Cochrane Collaboration) [14]. We expected that the data carried a certain amount of heterogeneity and therefore, a random-effects model was used. If the data were too heterogeneous for pooling based on methodological heterogeneity and statistical heterogeneity, we performed a descriptive review and summarized the available evidence.

RESULTS

Search and selection

A total of 1329 titles were retrieved; 343 articles were duplicates. Titles and abstracts of 986 unique reports were screened as displayed in **Figure 1**. After screening the full texts of 39 articles, 8 were selected for study assessment. Data on patients with MD was unavailable in one study. Despite attempts to contact the authors by email, we could not retrieve information about two potentially relevant articles. Data was unavailable with respect to patients with MD in one article and was therefore excluded for further assessments. Based on the independent selection of two reviewers (B.E. and E.S.), we selected five articles for our review [15-19]. Cross-reference checking did not reveal any additional relevant articles.

Data collection and analysis

Study characteristics are displayed in **Table 1**. Of the five studies included, two were prospective, randomised, controlled studies [15,19]. The study sample sizes ranged from to 15 to 360 patients. The cumulative number of participants was 498. The included studies were all monocentric and took place in Brazil, the USA, Belgium, Spain and the UK.

Garcia *et al.* [15] used the 'definite' diagnostic criteria for MD of the AAO-HNS 1995 [2]. Patients were included if they suffered from either unilateral or bilateral MD and had dizziness complaints in the disease's intercritical periods. Twenty-three randomised cases received virtual reality stimuli in a Balance Rehabilitation Unit (BRU) and balance rehabilitation exercises next to daily administration of betahistine and dietary modification.

The remaining 21 patients were only treated with betahistine and dietary modifications (mean age of 47.7 (range 20 to 60)).

In the study by Yardley *et al.* [19], 120 patients were recruited from the Menière's Society (n=4800) who were randomised into either the VR booklet (daily balance training exercises at home), the SC booklet (relaxation and controlled breathing exercises) or waiting list control (n=360, mean age 58±11.4). Symptoms were evaluated at baseline, at 3 and at 6 months.

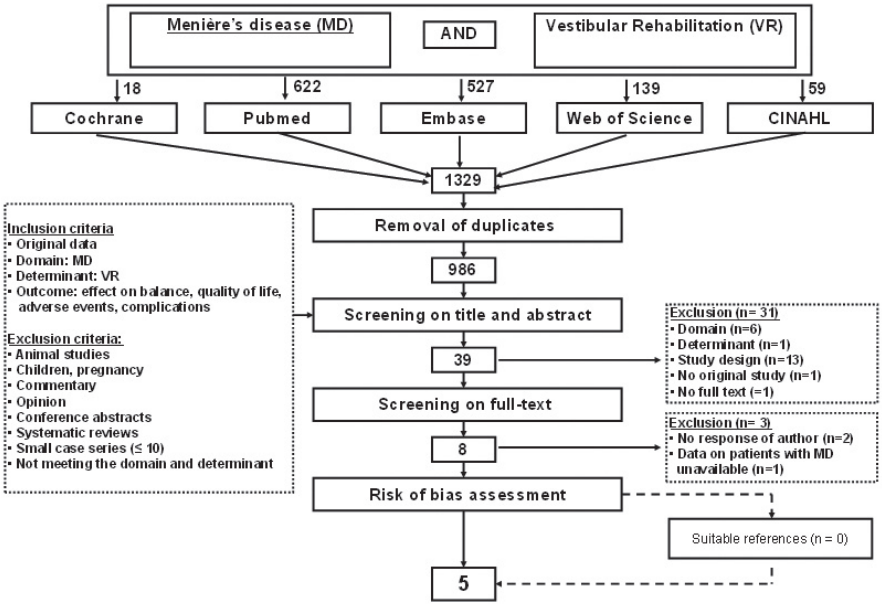

Figure 1. Flowchart for the selection of studies on the effect of vestibular rehabilitation for patients with Menière's disease.

Two of the cohort studies, Gottshall *et al.*[16] and Perez *et al.*[18], included patients meeting the criteria for 'definite' MD in line with the 1995 AAO-HNS guideline. Gottshall *et al.*[16] included 26 patients who had been free of vertigo attacks in the last 3 months. They measured the effect of various walking exercises (soft surfaces, walking stairs, eyes closed), vestibulo-ocular reflex exercises, cervical-ocular and depth perception exercises after 8 weeks on the Activities Balance Confidence (ABC) scale, the Dynamic Gait Index (DGI), the Computerized Dynamic Posturography (CDP) sensory organization test and the Dizziness Handicap Inventory (DHI). Perez *et al.*[18] included 15 MD patients free of vertigo spells in the previous seven months. Six patients were treated with intratympanic

gentamicin and nine with surgical labyrinthectomy. The VR program of 5 weeks contained weight-shifting exercises (static and dynamic balance tasks) and mobility training expressed as the Limits of Stability (LOS) and Sensory Organization Test (SOT) on the CDP. Nyabenda *et al.*[17] included 23 unilateral MD patients who met the stadium 3 criteria as defined by Arenberg *et al.*[20]. Results of rotational stimuli were investigated by means of vestibulospinal function tests, rotational tests and the DHI.

Results on balance

Garcia *et al.*[15] found no statistically significant differences between cases and controls based on BRU posturography results. The study by Gottshall *et al.*[16] reported an improvement of 12% on the DGI and the CDP improved with 25%. Perez *et al.*[18] reported a significant improvement on the LOS and SOT based on evaluation by the CDP. To improve symmetry of the nystagmic responses, Nyabenda *et al.*[17] found that a mean of 11.3±3.3 sessions (12 minutes per session) was required. Study results are summarized and displayed in **Table 2.**

TABLE 1. Study characteristics of selected studies on vestibular rehabilitation in Menière's disease.

Study	Design	Sample size (n)	♂ (%); Mean age[3]± /(min-max)	Type of MD	Uni-/ bilateral	VR exercises	VR program schedule	Control group intervention	Outcomes on balance	Outcomes on QoL	Therapy duration	Follow-up
Garcia *et al.* 2013[15]	RCT[1]	44	9(39); 47.7(20-60)	Definite MD	Uni- or bilateral MD	Betahistine 48 mg/ day, dietary modifications + Visual stimuli in [5]BRU and rehabilitation exercises	Twice/week, 12 sessions, 45 min/ session	Betahistine 48 mg/ day, dietary modifications	Posturography (center of pressure area)	[6]DHI, [7]DAS	6 weeks	NR
Gottshall *et al.* 2005[16]	CS	26	11 (42); 39(21-60)	Definite MD	[4]NR	Walking exercises, aerobics at home	Once/week, 8 sessions, duration of session NR	None	[8]DGI, [9]CDP	DHI, [10]ABC	8 weeks	12 months
Nyabenda *et al.* 2003[17]	CS[2]	23	8(35) ; 67.3(43-79)	Definite MD	Unilateral	Rotational and optokinetic stimuli	11±3 rotational stimuli sessions; optokinetic stimuli 3 ±10 min in n=7 patients	None	Vestibulospinal function tests, rotational tests	DHI	To attain improvement	36 months

Table 1. Continued.

Study	Design	Sample size (n)	♂ (%); Mean age[3]± /(min-max)	Type of MD	Uni-/ bilateral	VR exercises	VR program schedule	Control group intervention	Outcomes on balance	Outcomes on QoL	Therapy duration	Follow-up
Perez *et al.* 2006[18]	CS	37, MD 15	6(40); 56±5.6	Definite MD	Unilateral	Custom training, weight-shifting exercises, mobility training	10 sessions, 90 min/ session	None	[11]SOT score, [12]LOS score, CDP	DHI	5 weeks	12 months
Yardley *et al.* 2006[19]	RCT	360 (MD Society)	33 (28); 58±11.4	NR	NR	Vestibular rehabilitation booklet	Daily exercises, duration of session unknown	Symptom control booklet (relaxation, breathing exercises)	None	DHI, [13]VSS-SF, [14]DBQ	12 weeks	12 months

[1]=Randomised Controlled Trial; [2]=Prospective Cohort Study; [3]±SD=standard deviation; [4]NR = not reported; [5]BRU= Balance Rehabilitation Unit; [6]DHI=Dizziness Handicap Inventory; [7]DAS = dizziness analogue scale; [8]DGI= dynamic gait index; [9]CDP=computerized dynamic Posturography; [10]ABC = Activities Balance Confidence scale; [11]Sensory Organized Test score= SOT score; [12]LOS=limits of stability; [13]VSS-SF= Vertigo Symptom Scale-Short Form; [14]DBQ= Dizziness Beliefs Question

TABLE 2. Summary of results of included studies on balance.

Author, year	Outcome measure	Effect	P-value	Positive result
Garcia *et al.* 2013[15]	COP in cm^2 in the BRU with open and closed eyes, optokinetic reflexes and saccades (10 variables)	No significant differences on all variables	p>0.05	No favour for virtual reality & rehabilitation exercises over conservative therapy
Gottshall *et al.* 2005[16]	CDP Dynamic Gait Index	Improvement of 25% (51% to 69%) Improvement of 12%	?	?
Nyabenda *et al.* 2003[17]	Unterberger - Rotation Walking - Open eyes - Closed eyes Time for spinning sensations to disappear - Clockwise; with fixation - Counter clockwise; with fixation - Clockwise; without fixation - Counter clockwise; without fixation	Δ28(95%CI:8 to 47) Δ2(95%CI: 1 to 3) Δ22(95%CI: 12 to 32) Δ6(95%CI:4 to 9) Δ8(95%CI:4 to 11) Δ7(95%CI:4 to 9) Δ7(95%CI:3 to 11)	p=0.1 p<0.01 p<0.01 p<0.001 p<0.001 p<0.001 p<0.001	-
Perez *et al.* 2006[18]	CDP comprising SOT composite score (overall score) LOS: reaction time, sway velocity, endpoint excursion and directional control	Δ12(95%CI:-23 to -1)	*t*-test p=0.04; Wilcoxon test p<0.001 All LOS results Wilcoxon test p<0.001	-

NA= not applicable; COP= centre of pressure; CDP = computerized dynamic posturography; DGI: dynamic gait index; Sensory Organization Test; LOS: Limits of Stability.

Results on vertigo and (dizziness specific) quality of life

Study results on vertigo and dizziness specific quality of life are shown in **Table 3**. Garcia *et al.*[15] found a significant improvement of the Dizziness Analogue Scale in the cases and the control groups. DHI scores only improved significantly for the cases (DHI total mean difference 25.5 (95%CI:0.39 to12.0), DHI Emotional mean difference 10.5 (95%CI :4.9 to16.0), DHI Functional mean difference 7.83 (95%CI:2.2 to 13.4), DHI Physical mean difference 6.72 (95%CI:2.2 to 11.3)). Yardley *et al.*[19] found a significant improvement on the DHI after three months in the VR (mean difference -4.79 (-9.72 to -2.86)) and the SC booklet group (mean difference -1.18 (-2.52 to 0.16)). Results were not significantly better in the VR booklet group than in the control group. Improvement of the DHI was found in two cohort studies [16-18]. Gottshall *et al.*[16] reported that the mean DHI score decreased from 44.5 to 15.6, but no standard deviations were given. Based on the raw data, Perez *et al.*[18] found a median pre-treatment score of 48.0 (min 8.0-max 86.0) and a post-treatment score of median 32.0 (min 2.0-max 86.0) (Wilcoxon-test p=0.02). Nyabenda *et al.*[17] found no significant differences on the DHI scores before and after treatment.

Risk of bias

In line with the previously defined method, RCTs and cohort studies were analysed separately. Results on risk of bias assessment are displayed in **Table 4.** Statistical heterogeneity by means of the I^2 revealed a substantial risk of heterogeneity on balance and dizziness-related quality of life (I^2>50%). Based on the clinical and statistical heterogeneity, the high risk of bias, and the small number of selected studies, we concluded that it was not justifiable to pool the data.

None of the included studies had a low risk of bias on all domains. With regards to the RCTs, there was a low risk of bias on the random sequence generation, the selection of participants, the standardization of the outcome, incomplete data and selective reporting. Insufficient information was provided on the procedure of allocation concealment by Garcia *et al.*[15]. In both RCTs there was a high risk of bias on the blinding of participants. Yardley *et al.*[19] suffered from a high risk of bias on both the blinding of the outcome assessment and the standardization of the intervention. In the cohort studies, although the study protocols were unavailable, all data was systematically reported. Two studies suffered from a risk of bias on the standardization of the intervention and in one study there was a high risk of bias on incomplete outcome data.

TABLE 3. Summary of results of included studies on dizziness specific quality of life.

Author, year	Outcome measure	Intervention group		Control group		Effect size	P-value	Result
		Before therapy	After therapy	Before therapy	After therapy			
Garcia *et al.* 2013[15]	DHI (mean±SD) - Total - Emotional - Functional - Physical	57.6±21.3 17.9±8.6 22.8±10.0 17.0±7.3	*22.9±22.1 6.8±8.2 9.5±8.6 6.6±6.9	52.7±21.4 18.4±8.8 18.7±9.1 15.6±6.3	*48.4±22.4 17.3±9.8 17.3±8.4 13.3±8.0	*Δ25.5(95%CI:0.39 to 12.0) Δ10.5(95%CI :4.9 to 16.0) Δ7.83(95%CI:2.2 to 13.4) Δ6.72(95%CI :2.2 to 11.3)	p<0.001 p=0.001 p=0.004 p=0.003	Virtual reality & rehabilitation exercises over conservative therapy
Yardley *et al.* 2006[19]	DHI (mean±SD) - Total (baseline vs. 3 months)	52.25±21.19	*47.37±22.95	49.60±21.26	*48.17±11.76	Δ-0.8(95%CI- :-5.53 to 3.93)	p=0.738	VR booklet comparable to controls
Gottshall *et al.* 2005[16]	DHI (mean) - Total	44.5, no SD	15.6, no SD	NA	NA	-	-	-
Nyabenda *et al.* 2003[17]	DHI (mean±SD) - Total - Emotional - Functional - Physical	43.2±10.0 13.5±3.8 14.6±5.1 14.9±3.5	39.7±6.9 14.0±2.9 12.6±3.8 13.3±2.5	NA	NA	Δ3.5(95%CI:-1.6 to 8.6) Δ0.5(95%CI :-2.5 to 1.5) Δ2.0(95%CI:-0.6 to 4.7) Δ1.6(95%CI :-0.2 to 3.4)	p>0.05 p>0.05 p>0.05 p>0.05	-
Perez *et al.* 2006[18]	DHI - Total mean±SD - Total median(min-max)	51.2±20.9 48.0 (8.0-86.0)	37.3±29.3 32.0(2.0-86.0)	NA	NA	Δ13.9(95%CI:-5.6 to 32.9)	*t*-test p>0.05 Wilcoxon test p=0.02	-

*Independent *t*-test performed on intervention and control group after therapy, these analyses were not applicable (NA) for the uncontrolled studies.

TABLE 4. Risk of bias assessment of the selected studies.

		Relevance				Validity								
Author, year	**Design**	**Patients**	**Intervention**	**Outcome**		**Random sequence generation***	**Allocation concealment***	**Blinding of participant***	**Blinding of outcome assessment***	**Standardised selection of patients**	**Standardizes intervention**	**Standardised outcome**	**Incomplete outcome data**	**Selective reporting**
				Balance	QoL[1]									
Garcia *et al.* 2013[15]	RCT[2]	●	●	●	●	●	?	○	●	●	●	●	●	●
Yardley *et al.* 2006 [19]	RCT	?	●	●	●	●	●	○	○	●	○	●	●	●
Gottshall *et al.* 2005[16]	PCS[3]	●	●	●	●	NA[4]	NA	NA	NA	●	○	?	○	●
Nyabenda *et al.* 2003[17]	PCS	●	●	●	●	NA	NA	NA	NA	●	○	●	●	●
Perez *et al.* 2006[18]	PCS	●	●	○	●	NA	NA	NA	NA	?	●	●	●	●

* = Only applicable for studies using a randomised controlled design,[1]=Quality of Life; [2]=Randomised Controlled Trial; [3]=Prospective Cohort Study; [4]=Not applicable.

Grading studies on relevance and validity: ● = satisfactory on relevance or low risk of bias; ○ = unsatisfactory on relevance or high risk of bias; ? = unclear on relevance or unclear with respect to risk of bias.

DISCUSSION

The purpose of this systematic review was to evaluate the effect of VR for MD on balance and dizziness-related quality of life.

We found a scarce number of studies evaluating the effect of VR for MD. All studies, except for Yardley *et al.*[19], included patients who met the criteria for 'definite' MD as defined by the AAO-HNS in 1995. The results of the VR program were all measured on short term, varying from 6 to 12 weeks post-treatment, and the DHI was used in all studies to evaluate the effect on dizziness-related quality of life. Two cohort studies found a significant improvement on balance after VR therapy [17,18], but one RCT [15] and cohort study [16] failed to prove a beneficial effect of therapy. One RCT showed VR to be more effective than conservative treatment on improving dizziness-related quality of life [15],

whereas the remaining studies could not support this finding. In conclusion, there was inconsistent evidence regarding the effect of VR on balance and dizziness-related quality of life.

Unfortunately, data must be interpreted with caution because of methodological reasons. First and foremost, in none of the studies there was a low risk of bias. Yardley *et al.*[19] evaluated the effect of daily VR booklet exercises at home which makes the intervention less regulated and controllable. Only two of the included studies used a randomised controlled design and suffered from a risk of bias on allocation concealment or blinding. Cohort studies can be regarded as a less favourable design to evaluate the effect of interventions as influence of extraneous effects cannot be ruled out, limiting the level of evidence of these studies.

Secondly, the included studies varied with respect to the type of VR treatment, the frequency of the VR sessions, the outcome measures, especially on balance related outcomes. This, in part, yielded great variation in outcomes and introduced heterogeneity among the selected studies which prohibited us to pool data. With respect to dizziness-related quality of life, Fong *et al.*[20] evaluated the validity of patient-report outcome measures. Although the DHI, the ABC-scale and the Vertigo Symptom Scale-short form may be generalizable to other older age categories, none of these instruments were related to patients who suffer from age-related vestibular loss. Moreover, no set of objective outcome measures is developed for evaluation of outcomes on balance. In order to determine the effect of VR treatment, knowledge on normative values of age-related vestibular function on both objective and subjective outcome measures is essential [21].

Thirdly, Perez *et al.*[18] analysed effects of VR in MD patients who were previously treated with intratympanic injections with gentamicin or with surgical labyrinthectomy. Due to extirpation of the neuroepithelial elements of the diseases by these treatments, one may argue whether these patients still can be considered as MD patients. These patients, unless they have a known disease in the contralateral ear, are more akin to patients with a fixed vestibular deficit, for which VR has been shown to be helpful. This introduces significant heterogeneity and as these patients strictly do not meet the diagnostic criteria for MD this further call into question the relevance of their results for MD.

Fourthly, small sample sizes and wide confidence intervals were found in the included studies which creates imprecision.

Lastly, none of the selected studies reported on the incidence of adverse events or complications either in the short or in the long term. Moreover, none of the studies reported on any benefits over a longer period of time. In the majority of the studies effects were assessed at three, six or 12-months. Subanalysis with respect to trial adherence performed by Yardley *et al.*[19], suggested that compliance to the intervention increased positive outcomes due to the beliefs in effectiveness of the VR program. As a result, quantification

of effects in future trials should aim to assess individual experiences after VR interventions as those who can adhere to such programs are more likely to find some benefit.

Conclusion and recommendations for further research

In the current review, all studies suffered from a form of bias. Based on the low validity and inconsistent results of the selected studies we conclude that at this point the effect of VR in patients suffering from Menière's disease on balance and dizziness-related quality of life is inconclusive.

We recommend that future research should aim to use a randomised-controlled designed study and a common set of validated subjective and objective outcome measures to quantify the effect of VR treatment. In addition, it may be helpful to use a standardized set of VR treatment modalities as opposed to various techniques to create comparability between studies. To improve precision on assessment of effect, larger samples sizes are needed and the quality of studies may be improved by applying checklists such as the SPIRIT.

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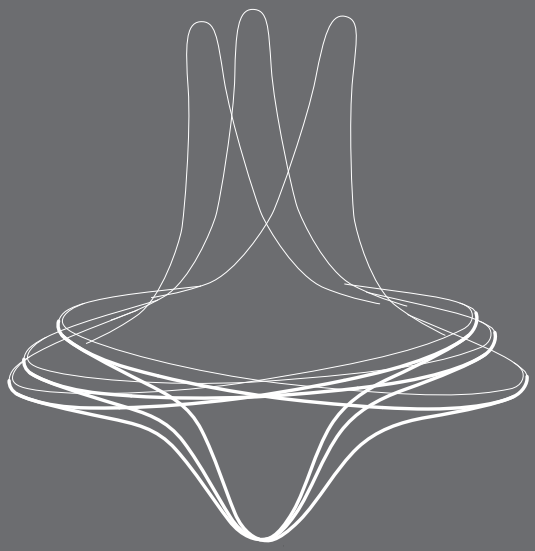
APPENDIX

Database	Search string	Result
Pubmed	((“Meniere Disease”[Mesh] OR “Endolymphatic Hydrops”[Mesh] OR Meniere*[tiab] OR Endolymphatic Hydrops[tiab] OR (Endolymphatic[tiab] AND Hydrops[tiab]) OR ((labyrinth*[tiab]) AND (Hydrops[tiab] OR “Syndrome”[Mesh] OR syndrome[tiab] OR syndromes[tiab] OR “Vertigo”[Mesh] OR vertigo[tiab] OR vertigos[tiab])) OR (Hydrops[tiab] AND (“Cochlea”[Mesh] OR Cochlea[tiab])) OR ((“Vertigo”[Mesh] OR vertigo[tiab] OR vertigos[tiab]) AND (auditory*[tiab] OR aural[tiab] OR otogenic*[tiab] OR labyrinth*[tiab])))) AND (((“Postural Balance”[Mesh] OR “Physical Therapy Modalities”[Mesh] OR “Physical Therapy Specialty”[Mesh] OR “Exercise Movement Techniques”[Mesh] OR “Exercise Therapy”[Mesh] OR “Exercise”[Mesh] OR “Rehabilitation”[Mesh] OR “Occupational Therapy”[Mesh])) OR (physiother*[tiab] OR Rehabilitation[tiab] OR habilitation[tiab] OR “Exercise Movement Technics”[tiab] OR “Exercise Therapy”[tiab] OR “Exercise Therapies”[tiab] OR “Occupational Therapy”[tiab] OR “Occupational Therapies”[tiab] OR “postural balance”[tiab] OR “adaptation exercises”[tiab] OR “adaptation exercise”[tiab] OR “vestibular rehabilitation”[tiab] OR “balance rehabilitation”[tiab] OR “balance training”[tiab] OR “vestibular adaptation”[tiab] OR “habituation exercises”[tiab] OR “habituation exercise”[tiab] OR “cawthorne”[tiab] OR “cooksey”[tiab] OR “booklet based”[tiab] OR “Physical Therapy”[tiab] OR “physical therapies”[tiab]))	622
Embase	((“Meniere Disease”/exp OR “Endolymphatic Hydrops”/exp OR Meniere*:ab,ti] OR Endolymphatic Hydrops:ab,ti OR (Endolymphatic:ab,ti AND Hydrops:ab,ti) OR ((labyrinth*:ab,ti) AND (Hydrops:ab,ti OR “Syndrome”/exp OR syndrome:ab,ti OR syndromes:ab,ti OR “Vertigo”/exp OR vertigo:ab,ti OR vertigos:ab,ti)) OR (Hydrops:ab,ti AND (“Cochlea”[Mesh] OR Cochlea:ab,ti)) OR ((“Vertigo”[Mesh] OR vertigo:ab,ti OR vertigos:ab,ti) AND (auditory*:ab,ti OR aural:ab,ti OR otogenic*:ab,ti OR labyrinth*:ab,ti)))) AND (((“Postural Balance”/exp OR “Physical Therapy Modalities”/exp OR “Physical Therapy Specialty”/exp OR “Exercise Movement Techniques”/exp OR “Exercise Therapy”/exp OR “Exercise”/exp OR “Rehabilitation”/exp OR “Occupational Therapy”/exp)) OR (physiother*:ab,ti OR rehabilitation:ab,ti OR habilitation:ab,ti OR “Exercise Movement Technics”:ab,ti OR “Exercise Therapy”:ab,ti OR “Exercise Therapies”:ab,ti OR “Occupational Therapy”:ab,ti OR “Occupational Therapies”:ab,ti OR “postural balance”:ab,ti OR “adaptation exercise*”:ab,ti OR “vestibular rehabilitation”:ab,ti OR “balance rehabilitation”:ab,ti OR “balance training”:ab,ti OR “vestibular adaptation”:ab,ti OR “habituation exercise*s” OR “cawthorne”:ab,ti OR “cooksey”:ab,ti OR “booklet based”:ab,ti OR “Physical Therapy”:ab,ti OR “physical therapies”:ab,ti))	527

Database	Search string	Result
Cochrane	(("Meniere Disease"/exp OR "Endolymphatic Hydrops"/ exp OR Meniere*:ti,ab OR Endolymphatic Hydrops:ti,ab OR (Endolymphatic:ti,ab AND Hydrops:ti,ab) OR ((labyrinth*:ti,ab) AND (Hydrops:ti,ab OR "Syndrome"/exp OR syndrome:ti,ab OR syndromes:ti,ab OR "Vertigo"/exp OR vertigo:ti,ab OR vertigos:ti,ab)) OR (Hydrops:ti,ab AND ("Cochlea"[Mesh] OR Cochlea:ti,ab)) OR (("Vertigo"/exp OR vertigo:ti,ab OR vertigos:ti,ab) AND (auditory*:ti,ab OR aural:ti,ab OR otogenic*:ti,ab OR labyrinth*:ti,ab)))) AND ((("Postural Balance"/exp OR "Physical Therapy Modalities"/ exp OR "Physical Therapy Specialty"/exp OR "Exercise Movement Techniques"/exp OR "Exercise Therapy"/exp OR "Exercise"/exp OR "Rehabilitation"/exp OR "Occupational Therapy"/exp)) OR (physiother*:ti,ab OR rehabilitation:ti,ab OR habilitation:ti,ab OR "Exercise Movement Technics":ti,ab OR "Exercise Therapy":ti,ab OR "Exercise Therapies":ti,ab OR "Occupational Therapy":ti,ab OR "Occupational Therapies":ti,ab OR "postural balance":ti,ab OR "adaptation exercise*":ti,ab OR "vestibular rehabilitation":ti,ab OR "balance rehabilitation":ti,ab OR "balance training":ti,ab OR "vestibular adaptation":ti,ab OR "habituation exercise*s":ti,ab OR "cawthorne":ti,ab OR "cooksey":ti,ab OR "booklet based":ti,ab OR "Physical Therapy":ti,ab OR "physical therapies":ti,ab))	18
Web of Science	((meniere) OR (endolymphatic hydrops) OR (endolymphatic AND hydrops) OR ((labyrinth*) AND (hydrops) OR (syndrome) OR (vertigo)) OR ((hydrops) AND (cochlea)) OR ((vertigo) AND ((auditory*) OR (aural) OR (otogenic) OR (labyrinth*))) AND ((("postural balance") OR ("Physical Therapy")OR ("Exercise Movement") OR ("Exercise therapy") OR ("Exercise") OR (rehabilitation) OR ("occupational therapy") OR (physiother*) OR (habilitation) OR ("exercise therapie*") OR ("exercise therapie*") OR ("occupational therapies") OR ("adaptation exercise*") OR ("adaptation exercise") OR ("adaptation exercises") OR ("vestibular rehabilitation") OR ("balance rehabilitation") OR ("balance training") OR ("vestibular adaptation") OR ("habituation exercises") OR ("habituation exercise") OR (cawthorne) OR (cooksey) OR ("booklet based") OR ("physical therapies"))	139

Database	Search string	Result
CINAHL	(MH "Meniere's Disease") OR (TI meniere OR AB meniere) OR Meniere* OR (MH "Endolymphatic Hydrops") OR (TI Endolymphatic OR AB Endolymphatic) OR ((TI labyrinth* OR AB labyrinth*) AND (TI hydrops OR AB hydrops OR (MH "Syndrome") OR TI syndrome OR AB syndrome OR TI syndromes OR AB syndromes OR (MH "Vertigo") OR TI vertigo OR AB vertigo OR TI vertigos OR AB vertigos)) OR ((TI hydrops OR AB hydrops) AND ((MH "Cochlea") OR TI cochlea OR AB cochlea)) OR (((MH "Vertigo") OR TI vertigo OR AB vertigo OR TI vertigos OR AB vertigos) AND (TI auditory OR AB auditory OR TI aural OR AB aural OR TI otogenic OR AB otogenic OR TI labyrinth* OR AB labyrinth*)) AND (TI "physical therapies" OR AB "physical therapies" OR TI "physical therapy" OR AB "physical therapy" OR TI "booklet based" OR AB "booklet based" OR TI cooksey OR AB cooksey OR TI cawthorne OR AB cawthorne OR TI "habituation exercises" OR AB "habituation exercises" OR TI "vestibular adaptation" OR AB "vestibular adaptation" OR TI "balance training" OR AB "balance training" OR TI "balance rehabilitation" OR AB "balance rehabilitation" OR TI "vestibular rehabilitation" OR AB "vestibular rehabilitation" OR TI "adaptation exercise" OR AB "adaptation exercise" OR TI "adaptation exercises" OR AB "adaptation exercises" OR TI "postural balance" OR AB "postural balance" OR TI "occupational therapy" OR AB "occupational therapy" OR TI "occupational therapies" OR AB "occupational therapies" OR TI "exercise therapies" OR AB "exercise therapies" OR TI "exercise therapy" OR AB "exercise therapy" OR TI habilitation OR AB habilitation OR TI rehabilitation OR AB rehabilitation OR TI physiother* OR AB physiother* OR (MH "Occupational Therapy") OR (MH "Rehabilitation") OR (MH "Exercise") OR (MH "Therapeutic Exercise") OR (MH "Physical Therapy") OR (MH "Balance, Postural"))AND (TI "physical therapies" OR AB "physical therapies" OR TI "physical therapy" OR AB "physical therapy" OR TI "booklet based" OR AB "booklet based" OR TI cooksey OR AB cooksey OR TI cawthorne OR AB cawthorne OR TI "habituation exercise* OR TI "vestibular adaptation" OR AB "vestibular adaptation" OR TI "balance training" OR AB "balance training" OR TI "balance rehabilitation" OR AB "balance rehabilitation" OR TI "vestibular rehabilitation" OR AB "vestibular rehabilitation" OR TI "adaptation exercise" OR AB "adaptation exercise" OR TI "adaptation exercises" OR AB "adaptation exercises" OR TI "postural balance" OR AB "postural balance" OR TI "occupational therapy" OR AB "occupational therapy" OR TI "occupational therapies" OR AB "occupational therapies" OR TI "exercise therapies" OR AB "exercise therapies" OR TI "exercise therapy" OR AB "exercise therapy" OR TI habilitation OR AB habilitation OR TI rehabilitation OR AB rehabilitation OR TI physiother* OR AB physiother* OR (MH "Rehabilitation") OR (MH "Therapeutic Exercise") OR (MH "Physical Therapy") OR (MH "Balance, Postural")))	59



9

BETAHISTINE IN MENIÈRE'S DISEASE OR SYNDROME: A SYSTEMATIC REVIEW

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Submitted

BACKGROUND

Menière's disease is characterised by recurrent episodes of vertigo, hearing loss and tinnitus, often with a feeling of fullness in the ear. Vertigo attacks can occur without warning and their intensity varies, which may lead to psychological suffering and a reduction in quality of life. To date, clinical therapy options include dietary modifications, intratympanic injections with methylprednisolone, dexamethasone or gentamicin, positive pressure therapy, endolymphatic sac decompression, endolymphatic duct blockage, ablative surgery such as vestibular nerve section or surgical labyrinthectomy and oral administration of betahistine. Betahistine dihydrochloride is an oral drug that has been prescribed to an estimated 130 million people worldwide since its first launch. Although betahistine has been used for vestibular vertigo in general it is thought by some clinicians to be specifically effective for Menière's disease. Nonetheless, no evidence for a benefit from the use of betahistine, despite its widespread use, especially in Europe. Reassessment of the effect of betahistine in the treatment of Menière's disease is therefore now warranted.

Objectives: To assess the effects of betahistine in patients with Menière disease or syndrome.

Search methods: Were performed by the Cochrane Ear, Nose and Throat Disorders Group (CENTDG) Information Specialist searched the Cochrane ENT Register; Central Register of Controlled Trials (CENTRAL); Ovid Medline; Ovid Embase; CINAHL; Web of Science; Clinicaltrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 16 January 2018 which was re-run on 29 January 2019.

Selection criteria: Randomised controlled trials (RCTs) evaluating patients with Menière's disease. We included studies in which the intervention involved betahistine and was compared to placebo. We evaluated all courses of betahistine: any dose regimes or formulations and for any duration of treatment.

Data collection and analysis: We used the standard methodological procedures expected by Cochrane. Our primary outcomes involved vertigo and significant adverse effect (upper gastrointestinal discomfort). Our secondary outcomes included hearing loss as measured by a pure-tone audiogram based on the four-tone average of thresholds at 0.5 kHz, 1 kHz, 2 kHz and 3 kHz, tinnitus measured by patient-reported questionnaire scores, aural fullness measured by patient-reported questionnaire scores, other adverse effects (headache and allergic skin reactions (pruritus, rashes)), and well-being and disease-specific health-related quality of life. We used GRADE to assess the quality of the evidence for each outcome.

Main results: We included 10 studies with a total of 402 participants. Four studies used a cross-over design and the remaining five were parallel-group RCTs. All studies were conducted in otorhinolaryngology departments within hospitals in Europe, the USA and Japan. All participants were adults with Ménière's disease, but different inclusion criteria and definitions for the disease were used. The daily dose of betahistine ranged between 16 mg and 144 mg. The risk of bias was unclear or high in all but one of the studies.

Primary outcomes: Although all of the included studies evaluated the effect of betahistine on vertigo, data pooling was not possible because of the heterogeneity in the evaluated participants and the lack of information about how they were diagnosed, the outcomes measured and the measurement methods used. One study with low risk of bias found no significant difference between the betahistine groups and placebo with respect to reduction in vertigo symptoms after a long-term follow-up period (more than three months). Two studies reported no significant difference in the incidence of upper gastrointestinal discomfort (low-certainty evidence).

Secondary outcomes: No differences in hearing loss, tinnitus or well-being and disease-specific health-related quality of life were found between the betahistine and placebo groups in any of the individual studies assessing these outcomes (low- to very low-certainty of evidence). Data on aural fullness could not be extracted from any of the studies.

The other adverse effect that was seen on the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effect on the long term included tinnitus, ear discomfort, nervous system disorders, headache, heartburn, skin rash, increased diuresis, extrasystoles and oral formication. The pooled risk ratio demonstrated a lower risk in favour of placebo over betahistine.

Authors' conclusions: High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, one study with low risk of bias found no evidence of a difference in the effect of betahistine on the primary outcome, vertigo, in patients with Ménière's disease when compared to placebo. Betahistine appears to be generally well tolerated and the risk of adverse effects on upper gastrointestinal discomfort is comparable to that of placebo. The main focus of future research should be on the use of comparable outcome measures across studies in order to increase homogeneity and therefore enable data pooling. This could be done by means of patient-reported outcome measures that have been developed and are used in other medical fields. A standardised method of designing and reporting trial results should be used, such as CONSORT.

PLAIN LANGUAGE SUMMARY

Background: Ménière's disease or syndrome is characterised by recurrent episodes of vertigo, hearing loss and tinnitus, often with a feeling of fullness in the ear. Vertigo attacks can occur without warning and their intensity varies. This may lead to psychological suffering and a significant reduction in quality of life. Current treatment options include dietary changes, intratympanic injections (through the ear drum) of steroids or antibiotics, positive pressure therapy (for example, the Meniett device), surgery and the drug betahistine (tablets). Betahistine has been used to treat vestibular vertigo in general, but it is thought by some clinicians to be specifically effective for Ménière's disease. The previous version of this Cochrane Review found no evidence of a benefit from the use of betahistine. However, it is still widely being prescribed to patients, especially in Europe. This new review therefore reassesses the effects of betahistine in the treatment of Ménière's disease.

Study characteristics: We found and included 10 randomised controlled trials with a total of 402 adult participants who suffered from Ménière's disease or syndrome. All studies compared the effect of betahistine to placebo. We looked at the effects of betahistine on vertigo symptoms, hearing, aural fullness, tinnitus and disease-specific quality of life. We also looked at adverse (side) effects.

Key results: Although all of the included studies evaluated the effect of betahistine on vertigo, we could not combine their results because of the differences in the participants evaluated and the lack of information about how patients with Ménière's disease were diagnosed, the outcomes measured and the measurement methods used. One study with a low risk of bias found no significant difference between the betahistine group and placebo groups with respect to reduction in vertigo symptoms after a long-term follow-up period (more than three months) (moderate-certainty of evidence). Two studies reported no significant difference in the incidence of the significant adverse effect upper gastrointestinal discomfort (low certainty of evidence). No differences in hearing loss, tinnitus or well-being and disease-specific health-related quality of life were found between the betahistine and placebo groups in any of the individual studies that assessed these outcomes (low- to very low-certainty evidence). Data on aural fullness could not be extracted from any of the studies.

The other adverse effect that was seen on the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effect on the long term included tinnitus, ear discomfort, nervous system disorders, headache, heart burn, skin rash, increased diuresis, extrasystoles

and oral formication. The pooled risk ratio demonstrated a lower risk in favour of placebo over betahistine.

Quality of the evidence: The overall certainty of evidence ranged from moderate to very low, although there was one high-quality study (with low risk of bias). In the remaining studies the risk of bias was generally unclear. In several (older) studies, it remained unclear how patients with Ménière's disease were diagnosed. The results of these studies may therefore not represent patients with Ménière's disease based on the diagnostic criteria that are currently used. The evidence in this review is up-to-date to January 2019.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Vertigo considering together intensity, frequency and duration of symptoms measured by a visual analogue scale (range 0 to 5, questionnaire) Follow-up: up to 3 months	Study population **167 per 1000**	**500 per 1000**	**RR 3.00** (0.97 to 9.30)	36 (1)	⊕⊕○○ LOW [1]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 333 more will have an improvement of vertigo than if they had taken placebo alone.
Vertigo considering together intensity, frequency and duration of symptoms vertigo considering together intensity, frequency and duration of symptoms (range 30-day interval vertigo rate, imbalance scores); Follow up: up to 9 months	Study population		Not estimable	259 (3)	⊕⊕⊕○ MODERATE [2]	Two studies out three studies found no significant difference between treatment with betahistine and placebo, including one high quality trial.

Betahistine compared with placebo for Menière's disease or syndrome						
Patient or population: Menière's disease **Setting:** Outpatient clinics **Intervention:** Betahistine **Comparison**: placebo						
Outcomes	**Illustrative comparative risks[*] (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Placebo	**Betahistine**				
Significant adverse (upper gastrointestinal discomfort (yes or no) Follow-up: up to 33 weeks	Study population **86 per 1000**	**83 per 1000**	**RR 0.86** (0.13 to 5.83)	37 (1)	⊕⊕○○ LOW [3]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 3 fewer will have a significant adverse effect than if they had taken placebo.
Hearing loss (improved: yes or no) Follow-Up: up to 2 weeks	Study population **56 per 1000**	**167 per 1000**	**RR 3.0** (0.34 to 26.19)	36 (1)	⊕⊕○○ LOW [1]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 111 more will have an improvement of hearing loss than if they had taken placebo.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Hearing loss (improved: yes or no) Follow-up: for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment	Study population **0 per 1000**	**200 per 1000**	**RR 3.0** (0.15 to 59.89)	10 (1)	⊕○○○ VERY LOW [4]	Non-significant difference between groups. If 1000 patients are treated with betahistine, 200 more will have an improvement of hearing loss than if they had taken placebo.
Hearing loss (measured by the adjusted mean change presented per frequency; mean hearing thresholds of 0.25 to 2 kHz) Follow-up: up to 9 months	The mean hearing loss score was 47.8 in the control group	The mean hearing loss score was 9.9 dB higher in the intervention group	**MD 10.10** (-0.97, 21.17)	35 (1)	⊕⊕○○ LOW [3]	Non-significant difference between groups, mean hearing loss score was 9.9 dB higher in the betahistine group.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Tinnitus (improved: yes or no) Follow-up: up to 12 weeks	Study population **167 per 1000**	**444 per 1000**	**RR 2.67** (0.84 to 8.46)	36 (1)	⨁⨁○○ LOW [1]	Non-significant difference. If 1000 patients are treated with betahistine 277 more will have an improvement of tinnitus than if they had taken placebo.
Tinnitus (improved: yes or no) Follow-up: for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment	Study population **1000 per 1000**	**1000 per 1000**	**RR 1.00** (0.71 to 1.41)	10 (1)	⨁○○○ VERY LOW [4]	Non-significant difference. If 1000 patients are treated with betahistine no difference will be seen in the effect on tinnitus compared to if they had taken placebo.

Betahistine compared with placebo for Menière's disease or syndrome

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Betahistine				
Tinnitus measured by the MiniTF questionnaire Follow-up: up to 9 months	The adjusted mean change was 0.67 (-0.049 to 0.182)	The adjusted treatment difference (95% CI) was 0.016 (-.0147 to 0.114) lower in the high dose betahistine group	**MD -0.16** (-0.48 to 0.17)	144 (1)	⊕⊕⊕○ MODERATE [2]	No significant difference between betahistine and placebo was seen on tinnitus as measured by the MiniFTF questionnaire.
Other adverse effects (yes or no) Follow-up: up to 3 months	Study population **167 per 1000**	**278 per 1000**	**RR 1.67** (0.47 to 5.96)	36 (1)	⊕⊕○○ LOW [1]	Non-significant difference. If 1000 patients are treated with betahistine, 111 more will have others adverse effects than if they had taken placebo.
Other adverse effects (yes or no) Follow-up: up to 9 months	Study population **61 per 1000**	**165 per 1000**	**RR 2.58** (1.21 to 5.49)	265 (3)	⊕⊕⊕○ MODERATE [5]	Significant difference. If 1000 patients are treated with betahistine, 104 more will have others adverse effects than if they had taken placebo.

Betahistine compared with placebo for Menière's disease or syndrome						
Patient or population: Menière's disease **Setting:** Outpatient clinics **Intervention:** Betahistine **Comparison**: placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Placebo	**Betahistine**				
Well-being and disease-specific quality of life based on visual analogue scale (3 point scale with three domains) Follow-up: 9 months	The adjusted mean change (95% CI) was -1.04 (-0.353 to 0.145)	The adjusted treatment difference (95% CI) was 0.025 (-0.267 to 0.217) lower in the high-dose betahistine group	**SMD 0.08** (-0.25 to 0.40)	144(1)	⊕⊕⊕○ MODERATE [2]	Non-significant difference. The adjusted treatment difference was 0.025 lower in the high dose betahistine group.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI; **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** standardized mean difference.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1Downgraded one level due to the use of non-validated outcome measures; downgraded one level due to imprecision.
2Downgraded one level due to the use of non-validated outcome measures.
3Downgraded one level due to study limitations (unclear risk of bias for sequence generation, allocation concealment and blinding); downgraded one level due to the level of uncertainty of the diagnosis (use of class II diagnostic criteria).
4Downgraded one level due to study limitations (unclear risk of bias for sequence generation, allocation concealment and blinding); downgraded one level due to the level of uncertainty of the diagnosis (use of class III diagnostic criteria); downgraded one level due to imprecision.
5Downgraded by one level due to inclusion of patients with a level of uncertainty of the diagnosis (use of class II diagnostic criteria)

BACKGROUND

Description of the condition

Menière's disease is characterised by recurrent episodes of vertigo, hearing loss and tinnitus, often with a feeling of fullness in the ear. Vertigo attacks can occur without warning and their intensity varies, which may lead to psychological suffering and a reduction in quality of life. The disorder may be subdivided into two categories: it may be secondary to a number of established inner ear disorders (Menière's syndrome) or idiopathic (Menière's disease). Menière's disease is known to be associated with endolymphatic hydrops, i.e. raised endolymph pressure in the membranous labyrinth of the inner ear [41]. However, hydrops per se does not explain all its clinical features. Nonetheless, both categories may be considered as one entity as in both endolymphatic hydrops is the pathophysiological hallmark of the disease.

The diagnostic process may be difficult as there is great variability in clinical presentation and no reference standard exists. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines [37] which have been revised twice [35,54]. The AAO-HNS 1995 guidelines formulate that a 'definite' diagnosis can be made on the basis of at least two spontaneous episodes of rotational vertigo lasting at least 20 minutes, audiometric confirmation of sensorineural hearing loss, plus tinnitus and/or a perception of aural fullness (**Appendix 1**). More recently diagnostic criteria have also been proposed by the Bárány Society [48].

In a recent study in the USA the prevalence of Menière's disease was estimated at 200 per 100,000 people per year [36]. Menière's disease is most common between 40 and 60 years of age [43]. Vertigo episodes tend to occur in clusters with a period of remission that may last for several months in between the clusters [55]. Episodes have been observed to occur with increasing frequency over the first few years after presentation and then decrease in association with a sustained deterioration in hearing [51]. In most cases, vertiginous episodes eventually cease completely [58]. The fluctuating, progressive and unpredictable natural history of Menière's disease makes investigation of any treatment effect difficult; studies therefore need to compare interventions with placebo over an adequate time period. The aim of treatment is: to reduce the number, severity and duration of attacks of vertigo; to prevent progression of the disease, the loss of hearing; and to alleviate any chronic symptoms (e.g. tinnitus and aural fullness).

Description of the intervention

Betahistine dihydrochloride (betahistine) is an oral drug that has been prescribed to an estimated 130 million people worldwide since its first launch [44]. Although betahistine has been used for vestibular vertigo in general [52], it is thought by some clinicians to be specifically effective for Menière's disease [53]. The recommended daily dose of betahistine

is 24 mg to 48 mg per day divided into two or three single doses containing 8 mg, 16 mg or 24 mg [44]. Although gastrointestinal side effects are cited in many formularies, the rate of adverse effects in patients taking betahistine is not significantly different from those taking placebo in comparison studies [52].

How the intervention might work

Betahistine is a weak histamine H1 receptor agonist and a potent histamine H3 receptor antagonist. The mechanism of action of the drug may be via the reduction of endolymphatic pressure through improved microvascular circulation in the stria vascularis of the cochlea [50]. In addition, inhibition of activity in the vestibular nuclei may contribute to rebalancing neural activity and expedite the recovery process [47, 60]. Studies have shown that betahistine reaches a peak plasma concentration in about one hour and it has a plasma half-life of approximately 3.5 hours. The maximal vestibular therapeutic effect will last approximately three to four hours (EMC 2015). The washout period can be calculated as four times the drug effect [57]. These pharmacological characteristics are thought to reduce the intensity and duration of vertigo symptoms in the short term (under three months) and additionally prevent attacks in the longer term (over three months).

Why it is important to do this review

The previous version of a Cochrane Review found insufficient evidence of a benefit from the use of betahistine [64]. Despite this, it is still widely used and studied in clinical practice, especially in Europe. Reassessment of the effect of betahistine in the treatment of Menière's disease is therefore now warranted.

OBJECTIVES

To assess the effects of betahistine in patients with either Menière's disease or Ménière's syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, including cluster-randomised controlled trials. We excluded quasi-randomised studies. Cross-over trials were eligible if data from before the cross-over were extractable, to avoid the potential for a carry-over phenomenon.

Types of participants

Patients with Menière's disease or syndrome. We classified studies according to the diagnostic criteria used for Menière's disease. We rated studies using the AAO-HNS or the Japanese Society of Equilibrium Research criteria to define probable, definite or certain Menière's disease's as class 'I' studies and studies using other diagnostic definitions as class 'II'. We rated studies including patients with 'possible' Ménière's disease as class 'III'. Studies including participants who had received treatment with betahistine in the past, were also eligible for inclusion.

Types of interventions

Betahistine: any dose regimes or formulations and for any duration of treatment. The sole comparison was: betahistine versus placebo. Concurrent use of other medication or other treatment was accepted if used equally in each group; for example, betahistine with an additional intervention versus placebo with an identical additional intervention. Where an additional intervention was used equally in both groups, we analysed this as a separate comparison. None of the selected studies evaluated the effect of betahistine by concurrent use of other treatment.

Types of outcome measures

We analysed the following outcomes in the review, but these were not used as a basis for including or excluding studies. Based on the pharmacological properties of the drug described above, we assessed outcomes as short-term (three months or under) or long-term (three months or over).

Primary outcomes

Vertigo: the proportion of patients with a reduction in vertigo symptoms (considering the intensity, frequency and duration of those symptoms altogether). Significant adverse effects: upper gastrointestinal discomfort.

Secondary outcomes

Hearing loss: the proportion of patients with progression of hearing loss (more than 15 dB), based on the four-tone average of thresholds at 0.5 kHz, 1 kHz, 2 kHz and 3 kHz, as measured by a pure-tone audiogram. Tinnitus: the proportion of patients with reduction of tinnitus, measured with patient-reported questionnaire scores such the Tinnitus Handicap Index (THI) ([45], see **Appendix 3**), the Tinnitus Functional Index [50], the Tinnitus Handicap Questionnaire [46], the Tinnitus Questionnaire [40], the Tinnitus Reaction Questionnaire [62] and the Tinnitus Severity Scale [59]. Aural fullness: the proportion of patients with reduction of aural fullness, measured by patient-reported questionnaire

scores (e.g. visual analogue scale).Other adverse effects: headache and allergic skin reactions (pruritus, rashes).Well-being and disease-specific health-related quality of life: overall changes as reported particularly on the Functional Level Scale (FLS) (see **Appendix 4**), the Menière's disease Patients Oriented Symptoms Severity Index (MPOSI) and the Dizziness Handicap Inventory (see **Appendix 5**). The FLS will be used as defined by the AAO-HNS 1995 guideline [35]. The questionnaires are validated and often used in trials to assess the change in dizziness-related and Menière's disease-related quality of life [38]. We anticipated that various non-validated tools (e.g. questionnaires) were used. We included validated tools only to ensure that the outcomes were as reliable as possible.

Search methods for identification of studies

The Cochrane Ear, Nose and Throat Disorders Group (CENTDG) Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 29 January 2019.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception: the Cochrane ENT Register (searched via Cochrane Register of Studies (CRS) to date);the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via CRS to 16 January 2018, re-run on 29 January 2019);Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 16 January 2018, re-run on 29 January 2019);Ovid EMBASE (1974 to 16 January 2018, re-run on 29 January 2019);LILACS (searched 16 January 2018, re-run on 29 January 2019);Web of Knowledge, Web of Science (1945 to 16 January 2018, re-run on 29 January 2019);ClinicalTrials.gov, www.clinicaltrials.gov (searched via the CRS to16 January 2018, re-run on 29 January 2019);World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (searched 16 January 2018, re-run on 29 January 2019). The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Box 6.4.b. (Handbook 2011). Search strategies for major databases including CENTRAL are provided in **Appendix 6.**

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched Ovid Medline to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials; and run none-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

Two authors (BE and HZ) independently selected studies to identify studies that appeared to meet the inclusion criteria. Both authors then reviewed the full-text articles of the retrieved trials and applied the inclusion criteria independently. We resolved any discrepancies by discussion or, failing that, by consultation of one of the other authors (TB, LM, AJ, PB).

Data extraction and management

Two authors (BE and HZ) independently extracted data from the studies using standardised data forms. We extracted data so as to allow an intention-to-treat analysis. If necessary or if insufficient data were provided in the paper, we contacted the authors for further information.

With regard to subgroup analysis, we extracted data to allow grading of the diagnostic accuracy of the methods used to define the study population (see Types of participants), along with the duration of disease and treatment protocol (dose and duration of drug treatment). For the outcome 'proportion of patients with a reduction in vertigo symptoms', we sought to independently dichotomise these into 'improved' or 'not improved'. If we found studies with more than two groups (e.g. two or more active treatments compared to placebo), we extracted data from the intervention and placebo groups but we made a note of the additional arm(s). If betahistine doses differed among the intervention groups within a study, we extracted data on the highest dose and compared this to placebo. Extraction of data on co-morbidity involved, for example, the presence of migraine and benign paroxysmal positional vertigo (BPPV). For each study, we extracted the following information: study design; duration of study; randomisation; allocation concealment; number of participants; setting of study; diagnostic criteria; exclusion criteria; age and sex distribution of participants; country of recruitment; date of study; number of intervention groups; generic name of intervention; total dose per day (mg); method of administration; outcomes measured and definition of outcomes; missing data and final sample size; funding; conflict of interest (any author);concomitant treatment.

Assessment of risk of bias in included studies

BE and HZ assessed the risk of bias of the included studies independently as guided by the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011). The 'Risk of bias' tool addresses the following domains: sequence generation; allocation concealment; blinding; selective outcome reporting; incomplete outcome data; and other sources of bias (e.g. improper statistical analysis).

The two authors judged these domains using the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involved describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. We resolved differences of opinion by discussion. If no consensus was reached, one of the other authors was consulted.

Measures of treatment effect

The primary outcome in this review was the proportion of participants with a reduction in vertigo symptoms, which is a dichotomised measure. For this type of data, we aimed to calculate the risk ratio (RR). For intervention-effect-measures using continuous data we planned to calculate the mean difference (MD) between groups, provided that the selected studies used the same scale of measurement and a validated tool. If different scales were used, we planned to calculate the standardised mean difference (SMD). For studies with ordinal data we planned to dichotomise these data wherever possible.

Unit of analysis issues

Cluster-randomised trials

We planned to include cluster-RCTs with the cluster as the unit of analysis. However, none of the included studies were cluster-randomised trials.

Cross-over trials

In Menière's disease it is unlikely that symptom activity returns to its baseline level after the first treatment period. Therefore, we only used data from cross-over trials only if the data prior to the cross-over could be obtained.

Multi-arm studies

In the event that we found studies with more than two groups (e.g. two or more active treatments being tested against placebo), we established which of the comparisons were relevant to the systematic review. We found only one multi-armed study that used independent groups of participants. As a result, participants were not included in more than one group and were treated as independent comparisons.

Repeated observations on participants

The unit of analysis was the participant. We did not anticipate that by-ear reporting was available but data per ear were preferred in cases of bilateral Menière's disease. We regarded bilateral Menière's disease patients as 'improved' if any ear showed no deterioration of hearing loss and the proportion of patients who had a reduction in tinnitus or aural fullness increased. If studies evaluated the effect over a longer time period, we recorded the results at multiple time points. To avoid unit of analysis error when combining study results in a single meta-analysis (and therefore counting the same participants in more than one comparison), we defined different outcomes related to the periods of follow-up and we performed separate analyses.

Dealing with missing data

Where necessary and where sufficient data from the study were not provided, we contacted the authors of the study requesting further details about missing data and reasons for the incompleteness of the data, in all those cases in which an email address was reported.
We were alert to potential mislabelling or non-identification of standard errors and standard deviations. Our methods for imputation were according to chapter 7.7.3 of the Cochrane Handbook for Systematic Reviews of Interventions [42]. If data were missing we used available case analysis using all data (as reported) for all randomised patients available at the end of the study/time point of interest, regardless of the actual treatment received. We considered the quality of outcome assessment as a study limitation (GRADE) and not as a stratifying factor. Unfortunately, we did not receive a useful response in any of the cases in which we contacted the authors. We did not impute missing data as it remained unclear whether data was missing ' at random' or ' not at random'.

Assessment of heterogeneity

We determined whether the selected studies suffered from clinical, statistical or methodological heterogeneity. We planned to quantify statistical heterogeneity using the I^2 statistic and the Chi2 test. With respect to the I^2 statistic, an approximate guide to interpretation is provided in the Cochrane Handbook for Systematic Reviews of Interventions [42]. If the I2 value was 50% or higher, we considered the data to suffer from substantial or considerable heterogeneity. For the Chi2 test, we used the indicator that if the Chi2 was greater than the degrees of freedom, then heterogeneity was likely to be present. We considered heterogeneity to be statistically significant if the P value was less than 0.10. Subsequently, we performed the meta-analysis using fixed-effect (in the absence of heterogeneity) and random-effects modelling (in the presence of heterogeneity).

Assessment of reporting biases

If an outcome was reported by at least 10 studies, we planned to assess publication bias using a funnel plot and Egger's test. Unfortunately, none of the outcomes were reported in this number of studies.

Data synthesis

We planned to analyse treatment differences as a risk ratio (RR), calculated using the Mantel-Haenszel method. Unfortunately, none of the selected studies analysed the outcomes by means of comparable or validated tools.

Subgroup analysis and investigation of heterogeneity

There were insufficient data available for subgroup analyses. Although we planned to perform the following subgroup analyses we were not able to do so for: stage of disease, as defined by the AAO-HNS 1995 guidelines (see **Appendix 7**); type of Menière's disease (see Types of participants); and dose of betahistine administered (minimum daily dose of 8 mg to a maximum of 148 mg).

Sensitivity analysis

We planned to conduct a sensitivity analysis by excluding those studies with a high risk of bias, thereby checking the robustness of the conclusion from the studies included in the meta-analysis. In addition, we planned to use sensitivity analyses for studies in which data were imputed. However, all but one study carried an unclear or high risk of bias and in none of the studies data were imputed.

GRADE and 'Summary of findings' table

Two authors (BE and HZ) independently used the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct, and we applied this in the interpretation of results. There are four possible ratings of quality: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that we are very uncertain about any estimate of effect obtained. The GRADE approach rates evidence from RCTs that do not have serious limitations, as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision; and publication bias. We included a 'Summary of findings' table for our comparison of betahistine versus placebo, constructed according to the recommendations

described in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions [42] for the following outcomes in the 'Summary of findings' table: the primary outcomes vertigo (the proportion of patients with a reduction in vertigo symptoms) and significant adverse events (upper gastrointestinal discomfort), and the secondary outcomes hearing loss, tinnitus, aural fullness, other adverse effects (headache and allergic skin reaction) and well-being and disease-specific health-related quality of life.

RESULTS

Results of the search

The electronic database search was performed by the Cochrane ENT Information Specialist on 29 January 2019 and identified 1130 records in total. No additional records were identified through other sources. This number dropped to 733 after the removal of duplicates. We screened the 733 records and found 710 to be irrelevant. We were left with 23 potentially eligible studies. We excluded 13 of these studies with reasons (see **Excluded studies**). We identified 10 studies meeting the inclusion criteria in terms of study design, participants and interventions. No further eligible records were identified from a handsearch of the reference lists. There are no studies awaiting assessment and we identified no ongoing studies. The study selection process is shown in shown in **Figure 1.**

Included studies

We included 10 randomised controlled trials, the details of which are shown in the Characteristics of included studies table. One of the included studies included more than two treatment arms [1]. Adrion *et al.* was a three-armed study that compared high-dose betahistine, low-dose betahistine and placebo. This was also the only study to highlight no financial conflict of interest. We identified no unpublished industry studies.

Design

In five out of 10 studies a prospective, cross-over comparison design was used [2,3,4,5,10]. In two of these five studies data prior to crossover were extractable. In the remaining five studies a parallel group design was used. All studies were described as being double blinded.

Sample sizes

The sample size ranged from 10 [8] to 221 [1]. A total of 402 patients had results reported across the 10 included studies. No additional results from unpublished studies were included in this review.

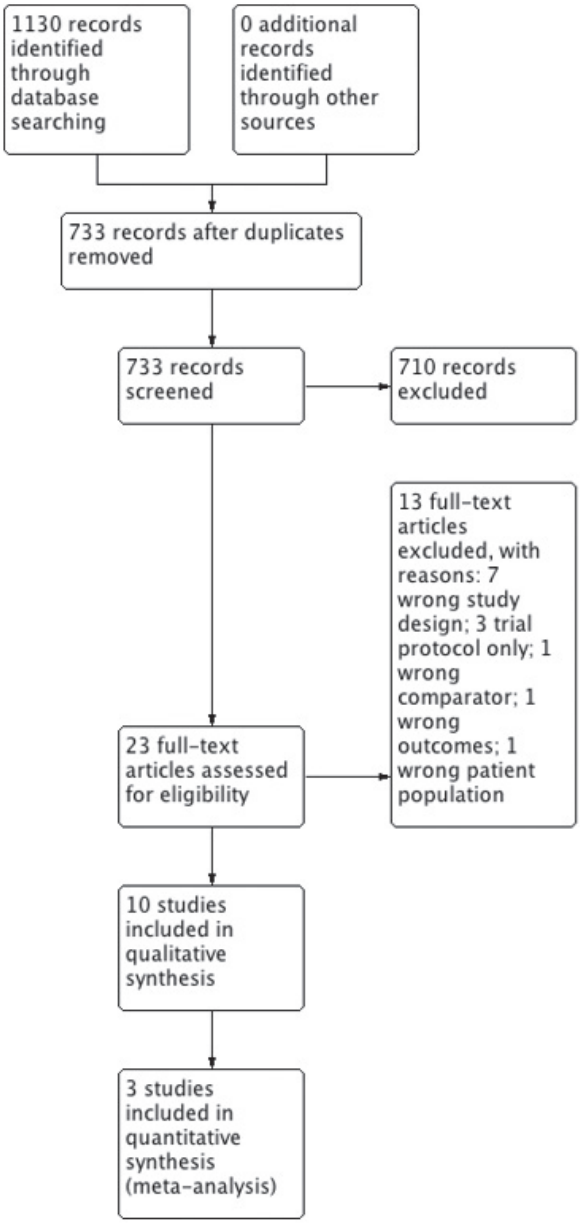

Figure 1. Process for sifting search results and selecting studies for inclusion

Setting

All studies were conducted in otorhinolaryngology departments within hospitals. The majority of the studies were single-centred. Adrion *et al.* and Mira *et al.* were multicentre studies [1,6]. The selected studies took place in Germany [1,5], the UK [2,4], the USA [3], Italy [6,8,9], Japan [7] and the Netherlands [10].

Participants

All of the included studies described the recruited patients as having Ménière's disease but different inclusion criteria and definitions for the disease were used. Adrion *et al.* applied the internationally recognised criteria for 'definite' Ménière's disease and was therefore classified as class 'I' (see Types of participants) [1]. Both Mira *et al.* and Schmidt *et al.* used other diagnostic definitions, including patients with probable/possible Ménière's disease according to the AAO-HNS criteria and the Utrecht working definition and we therefore classified them as class 'II' [6,10]. We classified Burkin *et al.*, Elia *et al.*, Frew *et al.*, Meyer *et al.*, Okamato *et al.*, Ricci *et al.* and Salami *et al.* as class 'III' since no specific predefined diagnostic criteria were provided or details of how vertigo attacks, hearing loss and tinnitus were evaluated [2-5,7-9].

Interventions and comparisons

All included studies evaluated the effect of betahistine. The daily betahistine dose that was used in the included studies varied: 16 mg [2,3], 24 mg [9], 2 mg [4,6], 36 mg [5,7](two times daily with three pills), 72 mg [10] and 144 mg [8]. One study compared high-dose betahistine (144 mg per day, in three doses) and low-dose betahistine (48 mg per day, in two doses) to placebo [1]. Schmidt *et al.* used a slow release formulation [10]. Assessment with regards to compliance was only reported in detail by Adrion *et al.*[1]. None of the selected studies evaluated the effect of betahistine with concurrent use of other treatment. All studies used a placebo as the comparator.

Outcomes

Most of the selected studies only evaluated short-term effects (less than three months), except for Adrion *et al.*, Mira *et al.* and Schmidt *et al.* [1,6,10]. Adrion *et al.* evaluated the effects of all three interventions arms after nine months, whereas Schmidt *et al.* defined a follow-up period of eight months [1,10]. Mira *et al.* assessed the effects after three months [6]. All included studies used one of our pre-specified outcome measures (Types of outcome measures).

Vertigo considering together intensity, frequency and duration of symptoms

All of the included studies included vertigo as one of their outcomes in the follow-up analyses. None of the included studies used the AAO-HNS diagnostic guideline to classify the frequency of vertigo attacks. In three studies the frequency of attacks was used as the main outcome to measure the effect of betahistine after a long-term follow-up (three months or more) in which all studies used different definitions to quantify the attack frequency, namely: the log-transformed number of attacks per 30-day interval based on daily diary reports, the number of vertigo attacks per month and the imbalance scores based on the number of attacks multiplying the number by 1, 4 or 9 for a mild, moderate or severe attack, respectively [1,6,10]. Burkin *et al.* quantified whether patients experienced dizziness or not, while Elia *et al.* based the effect of treatment on a subjective scale, which ranged from 0 to 3 [2,3]. The remaining studies used different ordinal scales to quantify the severity/intensity of the vertigo attacks by means of four-point scale [4], a five-point scale [5], a three-point scale [7], and a vertigo maximum intensity of the episode and the mean duration of each vertigo episode [9]. Ricci *et al.* used the AAOO classification in which both the effect on vertigo and hearing were combined and classified into four groups (A to D) [8].

Significant adverse effects: upper gastrointestinal discomfort

The incidence of upper gastrointestinal discomfort was reported by two studies [6,10], which both assessed the effect of betahistine in the long term (three months or more).

Hearing loss

The effect of betahistine on hearing loss was assessed in seven studies in variable ways. Adrion *et al.* reported results of pure tone audiometry per frequency (250 Hz, 500 Hz, 1000 Hz and 2000 Hz) and reported the adjusted mean change for placebo; these were compared with the adjusted mean difference for the low dose and high-dose betahistine [1]. Frew *et al.* reported the amount of deafness by means of a four-point scale without any further details [4]. Meyer *et al.* reported the mean frequency scores with standard deviation based on the three-point threshold of 0.5 Hz, 1.0 Hz and 2.0 kHz [5]. Okamato *et al.* used a three-point scale by which subjective changes in hearing were assessed [7]. The mean threshold for the frequencies of 0.5 Hz, 1.0 Hz and 2.0 Hz were classified by the ANSI in the study of Ricci *et al.* resulting in six classes (0 to 25 dB = normal, 26 to 40 dB = mild hearing loss, 41 to 55 dB = moderate hearing loss, 56 to 70 dB = moderately serious hearing loss; 71 to 90 dB = serious hearing loss; 91 dB = very serious hearing loss) [8]. Salami *et al.* used the mean threshold at frequencies of 0.25 kHz, 0.5 kHz, 1.0 kHz and 2.0 kHz but no mean and standard deviations were reported [9]. Schmidt *et al.* used the mean threshold scores based on the frequencies from 0.25 kHz to 2 kHz [10].

Tinnitus

All but one study reported changes in tinnitus symptoms before and after treatment [2]. Adrion *et al.* used the MiniTF questionnaire, where as Elia *et al.* used a subjective scale that ranged from 0 to 3 (3 = incapacitating, 2 = severe, 1 = moderate, 0 = not present) [1,3]. Frew *et al.* used a four-point scale, Meyer *et al.* a five-point scale and Okamato *et al.* a three-point scale [4,5,7]. Mira *et al.* reported tinnitus as part of the 'associated symptoms' which all together were scored with aural fullness, nausea and vomiting by means of four-point scale (0 = absent, 1 = mild, 2 = severe, 3 =disabling) [6]. Both Ricci *et al.* and Salami *et al.* used a scale ranging from 0 to 6, whereas Schmidt *et al.* used a four-point scale and the minimum masking level in dB with mean and standard deviations to assess the effect on tinnitus [8,9,10].

Aural fullness

Aural fullness was reported by seven of the selected studies, except for Burkin *et al.* and Okamato *et al.* [2,7] Adrion *et al.* reported that participants were instructed to record co-existing symptoms such as aural fullness but data were not shown in the results section [1]. In line with previous outcomes Frew *et al.* used a four-point scale and Meyer *et al.* a five-point scale [4,5]. In line with the tinnitus outcome Mira *et al.* reported aural fullness as part of the 'associated symptoms' questionnaire [6]. Both Ricci *et al.* and Salami *et al.* again used a scale ranging from 0 to 6 [8,9]. Aural fullness was evaluated in Schmidt *et al.* by means of a scale ranging from none to mild, moderate or severe, similar to tinnitus.

Other adverse effects

The incidence of other adverse effects was reported by four studies [1,6,7,10]

Well-being and disease-specific health-related quality of life

The effect on well-being was evaluated in two studies [1,6]. Adrion *et al.* used the Dizziness Handicap Inventory (DHI) whereas Mira *et al.* used the DHI, the vestibular disorders activities of daily living (VDADL) and the disease-specific health-related quality of life questionnaire.

Excluded studies

We excluded 13 studies for several reasons: duplicate publication (based on the available information full texts were checked), wrong study design, wrong comparator and wrong patient population (see Characteristics of excluded studies table).

Risk of bias in included studies

Two authors (BE and HZ) critically reviewed the studies for risk of bias. Where necessary, authors were contacted if we felt more detailed information on the methodology was required. In general, random sequence generation, allocation concealment and blinding of participant and personnel and outcome assessment were not reported clearly. This can be seen in the number of unclear scores regarding these matters (see Figure 2). All studies were reported to be double blinded whereas only Adrion *et al.* and Okamato *et al.* reported in detail how blinding was accomplished [1,7]. Many studies had incomplete outcome data and other sources of bias, resulting in high risk of bias scores. The characteristics of each trial are listed in the 'Characteristics of included studies' table and results on risk of bias are summarised in **Figure 2** and **Figure 3**.

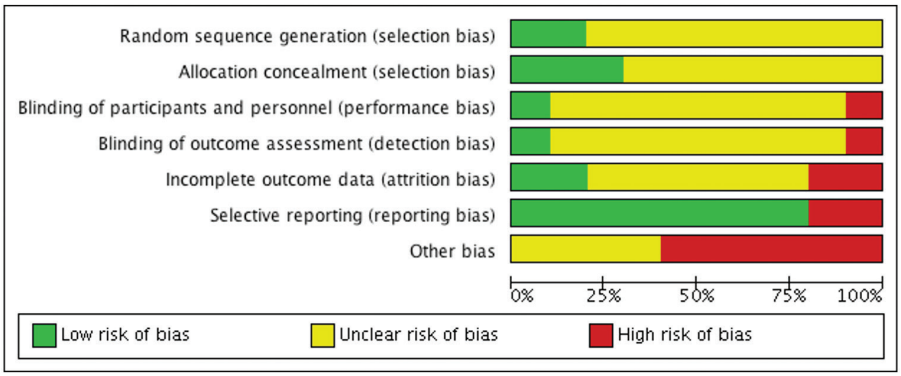

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Sequence generation

We considered the risk of selection bias due to inadequate method description on sequence generation to be unclear in seven studies [2,3,4,5,6,9,10] and low in the remaining three studies [1,7,8]. In the study performed by Adrion *et al.* a 1:1:1 ratio was used creating a high dose betahistine, low dose betahistine and placebo group [1]. Okamato *et al.* used a table of random numbers created by a third party independent from the medical institution [7]. Likewise, Ricci *et al.* assigned patients to the betahistine or placebo group based on a random list [8].

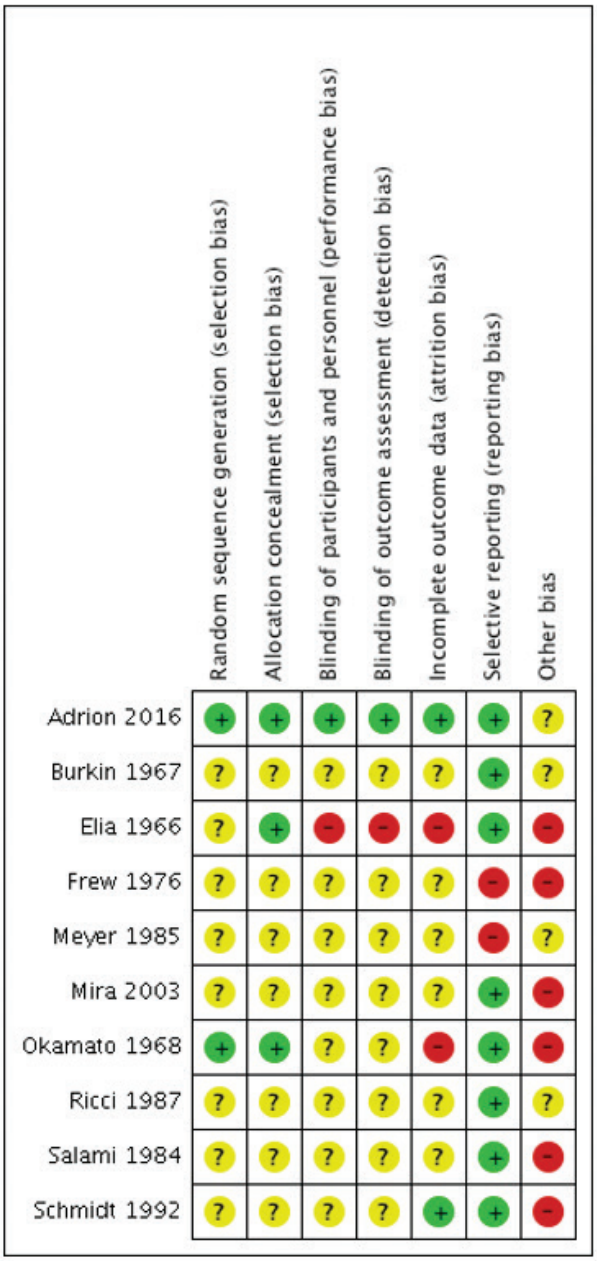

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation concealment

The allocation concealment was rated as unclear in all but three studies [1,3,7]. Elia *et al.* defined that a fifth person who was not involved in the study coded the tablets [3]. The treating physician, the statistician, the nurse and the patients were not aware of the given drug whereas the code was not broken until the final draft of this report. Adrion *et al.* described in detail that allocation concealment was performed by means of an Internet-based randomisation schedule which was generated by an investigator with no clinical involvement in the trial [1]. The patients, clinicians, core laboratories, and trial staff were all described as blinded to treatment allocation. Finally, Okamato *et al.* described that drug bottles were labelled with serial number according to the random layout list. The list was created at random by a third party [7].

Baseline characteristics

In two studies [3,4] no details on baseline characteristics were reported. Both studies were rated as "class III" with regards to the diagnostic criteria applied to include patients as Menière's disease. Although Okamato *et al.* described the sex distribution among the population, no information on age was given and unclear diagnostic criteria were used to describe the studies population (class III) [7]. With regards to the robustness of diagnostic criteria used to include patients with Ménière's disease, seven studies were rated as " class III" [2,3,4,5,7,8,9] two as "class II" [6,10] and one [1] as "class I". No significant differences were found in the studies that presented baseline characteristics for age and sex distribution [1,6, 8,9,10]. Only Adrion *et al.,* Ricci *et al.*; Salami *et al.* and Schmidt *et al.* reported the duration of disease before the start of the trial [1,8,9,10]. The effect of betahistine on hearing loss was objectively assessed by Adrion *et al.*, Ricci *et al.*; Salami *et al.* and Schmidt *et al.*, although specific hearing score outcomes were only given by Adrion *et al.* and Schmidt *et al.*.

Blinding

Due to inadequate blinding in seven out of the nine studies [2-6, 8-10], there was a risk of performance bias and detection bias in most studies. Although Elia *et al.* described that a fifth person coded the tablets given during trial execution the same sequence was repeated (A, B, C and D) was used in all patients [3]. As a result, the intervention could be predicted by the patients, physician or the statistician and was therefore considered to be of high risk. Ricci *et al.* described that a random list was used to divide participants but no information on blinding was provided in the methods section [8]. Therefore, we considered that there was still a considerable risk of inadequate blinding in both studies.

Incomplete outcome data

We considered only two studies to have a low risk of attrition bias [1,10] as concrete reasons of non-completion of the trial were given. In the studies performed by Burkin *et al.*, Frew *et al.*, Ricci *et al.* and Salami *et al.* there was no mentioning of dropping out or discontinuation of trial participation for any reason [2,4,8,9]. But as it remained unclear how many patients were analysed per outcome and only the level of significance was given, we assessed the risk of attrition bias to be unclear. The risk of attrition bias due to incomplete outcome data was high in Elia *et al.*, Meyer *et al.*; Mira *et al.* and Okamato *et al.* [3,5,6,7]. In the study performed by Elia *et al.*, four of 20 participants dropped out due to non-compliance to the trial and migration of participants [3]. In two patients, it remained unclear whether they had received betahistine or placebo. Meyer *et al.* reported a lower number of participants in some outcomes (for instance disturbed walking pattern) than in other outcomes, but no information was reported on this matter in the manuscript [5]. The participants studied by Mira *et al.* were not balanced across groups, for which they did not correct in the analyses. Last, Okamato *et al.* reported that four patients out of 36 dropped out (11%), not due to adverse effects of the drug use, but any other reason for drop-out was not clarified [7].

Selective reporting

A study protocol was available for the study performed by Adrion *et al.*, published prior to the execution of the study, from which we found that predefined outcomes were evaluated in the published version of the final manuscript, reporting on study results [1]. In seven studies, the outcomes that were mentioned in the abstract and/or methods section were also reported in the results section. Therefore, we considered the risk of selective reporting to be low in these studies [2,3,6,7,8,9,10]. The studies performed by Frew *et al.* and Meyer *et al.* mentioned outcomes in the method section that were not shown or described in the results section without reasoning and were considered to suffer from a high risk of selective reporting [4,5].

Other potential sources of bias

None of the studies had a low risk bias on other potential sources of bias. Adrion *et al.* did not reveal data on pre-randomisation attack frequency although it was considered as an inclusion criterion [1]. Data were not shown with respect to duration and age at the onset of disease although groups were reported to be balanced based on these characteristics thus it remained unclear whether this was performed properly. Although Burkin *et al.*, Elia *et al.*, Meyer *et al.*, Ricci *et al.* and Salami *et al.* reported no details on how statistical analysis was performed, the authors concluded that a positive effect was found of betahistine on symptoms of Menière's disease, this was considered to be a high potential source of bias [2,3,5,8,9]. Frew *et al.* used one-sided testing which should have been two-sided [4].

Moreover, standard deviations were not reported and we considered a high risk of selection bias due to a pre-treatment period, in which the investigator was allowed to exclude placebo responders hereby decreasing external validity of the study results. Sample size calculation performed by Mira *et al.* was done without referring to previous studies performed [6]. In the outcome section, improvement of associated symptoms including tinnitus, fullness of the ear, nausea and vomiting which were summarised in one figure. However, it was unclear how performed and whether data were complete. The trial medication during the execution of the trial by Okamato *et al.* was supplied by Eisai Co, the role of this subsidising party remained unclear [7]. We considered there was a high risk of bias in the study by Schmidt 1992 since the intention to treat analysis was not correctly executed because one patient crossed over due to side effects earlier than the protocol stated. Furthermore, the data were analysed per protocol [10]. Moreover, in these analyses the authors did not account for the loss of follow-up from drop-outs.

Effects of interventions

See: **Summary of findings table 1**.

Betahistine versus placebo

Primary outcomes

Proportion of patients with reduction in vertigo symptoms (considering together the intensity, frequency and duration of those symptoms)

All of the included studies evaluated the effect of betahistine on vertigo symptoms by means of different Likert-type scales or by using a mathematical formula, resulting in both dichotomous and continuous data; we therefore could not pool the data for this outcome. In addition, data from the first period could not be extracted from four cross-over studies [2-5]. Ricci *et al.* combined the effect on vertigo and hearing loss in one outcome and no numerical data were presented [8]. No data could be extracted from Salami *et al.* [9].

Short-term follow-up (less than three months)

Okamato *et al.* used a three-point visual analogue scale from which the proportion of patients with an improvement of vertigo symptoms at short-term follow-up was quantified. The risk ratio (RR) was 3.0 (95% confidence interval (CI) 0.97 to 9.30) in favour of betahistine (GRADE: low certainty) (**Analysis 1.1**) [7].

Long-term follow-up (more than three months)

Adrion *et al.*, Mira *et al.* and Schmidt *et al.* all assessed the effect of betahistine after a long-term follow-up [1,6,10]. Data could not be pooled because there was significant heterogeneity in outcomes between studies (**Analysis 1.2**) and no raw data to impute

standard deviations were available. Mira *et al.* described a significant improvement in the monthly vertigo attack frequency without presenting absolute baseline and endpoint data for the placebo group [6]. Schmidt *et al.* found no difference between the betahistine and placebo group in the effect on imbalance scores [10]. Adrion *et al.* was the study with the lowest risk of bias; this study found no favourable effect after comparing high-dose and low dose betahistine to placebo [1]. In summary, two studies found no favourable effect for betahistine which included one study with a high quality [1,10]. We assessed the certainty of the evidence for this outcome as moderate (GRADE).

Significant adverse effect: upper gastrointestinal discomfort

Both Mira *et al.* and Schmidt *et al.* reported no significant difference in the incidence of upper gastrointestinal discomfort. The pooled risk ratio was 0.86 (95% CI 0.13 to 5.83; 2 studies; 118 participants) in favour of placebo (**Analysis 1.3**) (GRADE: low certainty) [6,10].

Secondary outcomes

Hearing loss

Hearing loss was evaluated in both the short and long term by means of both dichotomous data (proportion of patients with improvement) [7,8] and continuous data based on means with corresponding four-point thresholds for the frequencies from 0.25 kHz to 2.0 kHz [10]. Data from the four remaining studies could not be pooled because only data per frequency were reported and no mean four-point threshold score could be calculated [1], no pre-cross over data were available [4,5], or no data were presented [9]. No significant difference between the betahistine and placebo group could be found in the included studies.

Short-term follow-up (less than three months)

In the short term, Okamato *et al.* reported a risk ratio of 3.00 (95% CI 0.34 to 26.19; 1 study; 36 participants) for the improvement of hearing (GRADE: low certainty) (**Analysis 1.4**) [7].

Long-term follow-up (more than three months)

The long-term effect on hearing loss was evaluated by Ricci *et al.*, which reported a risk ratio of 3.00 (95% CI 0.15 to 59.89; 1 study; 10 participants) (GRADE: very low certainty) (**Analysis 1.5**) [8]. Schmidt *et al.* found no difference between the betahistine group and the placebo group based on mean threshold scores at long-term follow-up (mean difference (MD) 10.10, 95% CI -0.97 to 21.17; 1 study; 35 participants) (GRADE: low certainty) (**Analysis 1.6**) [10].

Tinnitus

Short-term follow-up (less than three months)

The effect of betahistine on tinnitus was evaluated at short-term follow-up by Okamato *et al.*, which reported the proportion of participants with an improvement as a risk ratio of 2.67 (95% CI 0.84 to 8.46; 1 study; 36 participants) (GRADE: low certainty) (**Analysis 1.7**). These results are not statistically significant or clinically relevant [7].

Long-term follow-up (more than three months)

At long-term follow-up, Ricci *et al.* found no difference between the betahistine group and the placebo group based on the proportion of patients without deterioration of hearing (risk ratio 1.00, 95% CI 0.71 to 1.41; 1 study; 10 participants) (GRADE: very low certainty) (**Analysis 1.8**) [8]. Long-term effect was reported as the standardised mean difference based on the MiniTF in Adrion *et al.*, which found no difference in the difference between betahistine and placebo (SMD -0.16, 95% CI -0.48 to 0.17; 1 study; 144 participants) (GRADE: moderate certainty)(**Analysis 1.9**) [1].

Aural fullness

Data on aural fullness could not be extracted from any of the seven studies because first period, pre- cross-over data could not be extracted [4,5], no aural fullness data were presented [1], no numerical data were presented [9,10], data for the betahistine group and placebo group were not shown [8] or results were reported only with a P value without data on baseline absolute values and endpoint values [6].

Other adverse effects

The incidence of 'other' adverse effects was reported at both short and long-term follow-up which were dull headache, tinnitus, ear discomfort, nervous system disorders, headache, heart burn, skin rash, increased diuresis, extrasystoles and oral formication.

Short-term follow-up (less than three months)

Okamato *et al.* found no significant difference in other adverse effects between the betahistine and placebo group (RR 1.67, 95% CI 0.47 to 5.96; 1 study; 36 participants) (GRADE: low certainty) (**Analysis 1.10**) [7].

Long-term follow-up (more than three months)

At long-term follow-up, Adrion *et al.*, Mira *et al.* and Schmidt *et al.* found a lower risk ratio in favour of placebo when compared to betahistine [1,6,10]. The pooled risk ratio was 2.58 (95% CI 1.21 to 5.49; 3 studies; 265 participants) (GRADE: moderate certainty) (**Analysis 1.11**).

Well-being and disease-specific health-related quality of life

Disease-specific health-related quality of life was evaluated by Mira *et al.*, but because the results were reported only as percentage reductions without baseline absolute values and missing measures of spread, no useful data could be extracted [6]. Adrion *et al.*evaluated disease-specific health-related quality of life by means of the Dizziness Handicap Inventory (DHI) which were reported as standardized mean differences compared to placebo [1]. No significant difference between the placebo and high-dose betahistine group could be demonstrated (SMD 0.08, 95% CI -0.25 to 0.40; 1 study; 144 participants) GRADE: moderate certainty (**Analysis 1.12**).

DISCUSSION

Summary of main results

The current review includes 10 randomised controlled trials (RCTs), which evaluated the effects of betahistine compared to placebo in a total of 402 adult participants with Ménière's disease. For the primary outcome, the reduction of vertigo symptoms (considering together the intensity, frequency and duration of those symptoms) there was clinical heterogeneity between studies due to differences in the outcome measured and methods used. We could therefore not perform data pooling for this outcome. One adequately powered study with low risk of bias did not find evidence of a difference between the betahistine and placebo groups for this outcome [1]. We assessed the certainty of this evidence to be moderate (GRADE). No statistically significant or clinically relevant difference was found with respect to the significant adverse effect (upper gastrointestinal discomfort) in the two studies that reported this outcome [6,10]. No differences in hearing loss, tinnitus or well-being and disease specific health-related quality of life were found between the betahistine and placebo groups in any of the individual studies assessing these outcomes (low- to very low-certainty evidence). Aural fullness was evaluated by one study based a non-validated visual analogue scale which lacked information whether or not results were statistically better in the betahistine compared to the placebo group. The other adverse effect that was seen on the short term was a dull headache. No significant difference between the betahistine and the placebo groups (low-certainty evidence) could be demonstrated. Adverse effect on the long term included tinnitus, ear discomfort, nervous system disorders, headache, heartburn, skin rash, increased diuresis, extrasystoles and oral formication. The pooled risk ratio demonstrated a lower risk in favour of placebo over betahistine. High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, one study with low risk of bias found no evidence of a difference in the effect of betahistine on the primary outcome, vertigo, in patients with Ménière's disease when compared to placebo [1].

Overall completeness and applicability of evidence

Specific diagnostic criteria were used to select patients for trial participation in only one of the included studies [1]. In the remaining studies, either rather vague diagnostic criteria were applied, including recruiting patients with 'probable' Ménière's disease, or no details were provided about how patients were diagnosed with Ménière's disease. In particular, in the six studies involving 'class III' rated participants (see **Types of participants**), it remains disputable whether these patients can be considered to have Ménière's disease. The applicability of the evidence in these studies is therefore limited. In none of the included studies were data provided on the previous duration of the disease, including the frequency and intensity of attacks. Generally, in Ménière's disease vertigo attacks stop after approximately 5 to 15 years. It is therefore of great importance that this information is collected before trials are started to allow the interpretation of any observed treatment effect.

Quality of the evidence

The certainty of the evidence in this review ranged from moderate to very low, although one high-quality study was included [1]. Since none of the studies used similar methods to evaluate the effect of treatment on vertigo, it remains hard to assess whether the reported estimates are true. Future research should aim to use more standardised and comparable methods to assess the effect on vertigo in order to increases the level of evidence and allow more concrete conclusions to be drawn from the data. The certainty of the evidence was mainly negatively affected by study limitations (risk of bias), the low level of external validity and imprecision due to the small sample sizes. Studies lacked information on the selection procedure used to identify participants and methods were poorly reported, especially with respect to statistical analyses. In most studies it remained unclear how randomisation, allocation concealment, blinding of personnel, participants and outcome assessors were performed. Only one of the included studies had a pre-published protocol available for inspection.

Potential biases in the review process

We made no significant changes to our planned methods. We performed a comprehensive electronic database search. Language was not a barrier for inclusion and we reviewed full text articles in Japanese, German and Italian after these were translated. The roles of all authors were predefined before the start of the review process. Two authors selected studies for inclusion and judged risk of bias independently. Two authors independently extracted data to minimise personal bias. Both clinical and statistical heterogeneity were evaluated before considering quantitative analyses. The predefined outcome measures were as broad as possible, aiming to allow the summarising of data or make pooling of data more feasible.

Agreements and disagreements with other studies or reviews

At least two other reviews have evaluated the effect of betahistine in the treatment of Ménière's disease [47,53]. Both reviews concluded that there is a favourable effect of betahistine on vertigo. Lacour *et al.* is an expert opinion paper, which describes the definition of Ménière's disease, its epidemiology, pathophysiology and the role for betahistine in its therapeutic management including the mechanisms of action that are hypothesised to play a role in the potential positive effect of the drug [47]. The favourable clinical effect of betahistine is evaluated by means of a narrative summary of the results found in the Mira *et al.* study [6]. In addition, comparative studies and the results of an as yet unpublished open trial study are discussed. No data pooling or meta-analysis was performed. The authors concluded that betahistine is an effective therapy for Menière's disease and related conditions. Nauta *et al.* is a review and meta-analysis on patients with vestibular vertigo or Ménière's disease, which aimed to assess the "overall judgment of the investigator on the effectiveness of the drug treatment". Statistical analyses were performed to combine ordered categorical data. The overall random effect - the average odd ratio (OR) was 2.58 (95% confidence interval (CI) 1.67 to 3.99). When restricted sub-analyses of Ménière's disease patients only were performed the average OR was 3.37 (95% CI 2.14 to 5.29). No analysis of validity or risk of bias assessment was presented. Cochrane ENT has published two systematic review evaluating

the effects of betahistine for other clinical indications than Ménière's disease. One review evaluated the effect of betahistine on symptoms of vertigo, identifying 17 studies (1025 participants) [52]. Out of these 17 studies, five evaluated the effect of betahistine for Ménière's disease from which the pooled risk ratio was 1.56 (95% CI 0.92 to 2.62; 3 studies; 139 participants). Similar to the current review, the authors stated that results need to be interpreted with caution as the diagnoses differed between studies and did not necessarily meet standard diagnostic criteria. Moreover, the incidence of adverse effects was similar for both betahistine and placebo. The second review evaluated the effect of betahistine on tinnitus and included five studies (303 to 305 participants) [61]. This review concluded that there is no evidence to suggest that betahistine has an effect on subjective idiopathic tinnitus. In summary, previous reviews have either concluded that there is insufficient evidence to say whether betahistine has any effect on Ménière's disease or that there may be a positive effect of betahistine based low-quality studies so further research is likely to have an important impact on the interpretation of the results. In line with the findings of the current review, previous work has also concluded that betahistine is generally well tolerated with a similar risk of treatment-related adverse effects to placebo. Moreover, all previously evaluated studies included in reviews or meta-analyses have suffered from significant heterogeneity with respect to participants, dose of betahistine, follow-up duration and the methods of evaluation for outcomes.

AUTHORS CONCLUSIOSN

Implications for practice

High-quality studies evaluating the effect of betahistine on patients with Ménière's disease are lacking. However, one study with high quality found no evidence of a difference in the effect of betahistine on the primary outcome, vertigo, in patients with Ménière's disease when compared to placebo [1]. Betahistine appears to be generally well tolerated and the risk of gastro-intestinal discomfort is comparable to that of placebo. Further studies with a low risk of bias (in particular with respect to allocation and blinding) and rigorous inclusion criteria are required to independently verify the lack of evidence of a beneficial effect of betahistine for Ménière's disease compared to placebo. Patients considering treatment options should be informed about the findings of this review, which found no evidence of a beneficial effect of betahistine on the primary outcome, vertigo. Patients should also be informed that betahistine is generally well tolerated and the risk of adverse effects is low and comparable to that of placebo. Based on this information patients may still choose to start their treatment with betahistine, especially in the current absence of any other safe, non-invasive effective treatment that has high patient acceptability and relatively low cost, and is well supported by high-certainty evidence. Nonetheless, it remains questionable whether prescription of betahistine is justifiable or cost-effective. If patients decide to proceed with betahistine, a trial period of around three months could be offered. This period is sufficient to assess whether the patient experiences any beneficial effects on their symptoms or any adverse effects. If any unwanted effects outweigh any benefit, or there is no apparent improvement, therapy can be withdrawn.

Implications for research

Future research into the effectiveness of betahistine in patients with Ménière's disease should use rigorous methodology. Due to the subjective nature of most outcome measures, the risk of bias with respect to randomisation and blinding needs to be low to avoid any placebo effect. Standardised diagnostic criteria should be rigorously applied. A standardised method of designing and reporting trial results such as the CONSORT statement should be used (CONSORT 2010). We recommend validated, patient-centred outcome measures for research in the field of Ménière's disease. A core outcome set would be of particular value for this condition because of the multiple subjective symptoms that are characteristic. By means of a core outcome set a standardised set of outcomes would be reported, which would facilitate direct comparison between studies and the ability to perform data pooling. Due to the highly variable and poorly understood natural history of Ménière's disease, baseline characteristics and information on the natural course of the disease is of great importance for the interpretation of the treatment effects. For instance, information on the duration of disease, the frequency of vertigo attacks since the start of the disease, the

duration and intensity of the vertigo attacks, age and the amount of hearing loss may all be of value at the time of trial enrolment. Moreover, with the exception of the one high-quality study [1], none of the included studies in this review carried out an adequate power calculation before the start of trial. Future trials should include a power analysis to make sure that the estimated difference in effect between treatment arms can indeed be identified by the number of included participants. Research into the natural history of the condition via prospective longitudinal studies or registries would also be valuable in planning future clinical trials of therapy for Ménière's disease. However, in the light of limited means, as well as the huge effort involved in conducting a trial on the part of patients, doctors and researchers, as well as the very low estimated added value of betahistine in the treatment of Ménière's disease found in this review, we anticipate that research on this topic may not be prioritised

Acknowledgements
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CHARACTERISTICS OF INCLUDED STUDIES

Adrion 2016

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 221 participants were allocated to either betahistine high dose, low dose or placebo for a nine month follow-up; 74 were allocated to the placebo group, 73 to the low dose betahistine group and 74 to the high dose betahistine group. Number completed: 72 in the placebo group, 70 in the low dose betahistine group, 72 in the high dose betahistine group **Participants baseline characteristics**: Age: mean age for placebo 54.5 (SD 12.8), low dose betahistine 56.1 (SD 11.1), high dose betahistine 56.1 (SD 12.6)Gender: male (%) for placebo 35 (47), low dose betahistine 39 (53), high dose betahistine 35(47), total 109 (49). **Included criteria**: Patients aged 18-80 years were eligible for enrolment if they presented with two or more definitive spontaneous episodes of vertigo of at least 20 minutes' duration, had audiometrically documented hearing loss on at least one occasion, and tinnitus or aural full-ness in the treated ear, excluding other possible causes of vertigo. These factors made up a diagnosis of definite unilateral or bilateral Meniere's disease, fulfilling the criteria of the 1995 American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) guideline. Furthermore, patients had to be in an active phase of the disease, with at least two vertigo attacks per month in at least three consecutive months before enrolment. Female patients of childbearing potential were only included if they had a negative serum pregnancy test within seven days before initiation of treatment and were willing to practice acceptable methods of birth control during treatment and for three months after treatment; CLASS I. **Excluded criteria**: Exclusion criteria were diagnosis of other central or peripheral vestibular disorders such as vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, as well as phobic postural vertigo. Patients were excluded if they had known contra-indications or sensitivity to betahistine, such as bronchial asthma, pheochromocytoma, treatment with other antihistaminic drugs, ulcer of the stomach or duodenum, or severe dysfunction of liver or kidney. Safety-related exclusion criteria were severe coronary heart disease or heart failure, persistent uncontrolled hypertension with systolic blood pressure higher than 180 mm Hg or diastolic blood pressure higher than 110 mm Hg, life expectancy less than 12 months, other serious illness, or a complex disease that might confound treatment assessment. General exclusion criteria were participation in another trial with an investigational drug or device within the past 30 days, previous participation in the present study, or planned participation in another trial. **Pre-treatment:** Not reported.

Interventions	**Intervention group:** **Low dose betahistine: 2**4 mg per capsule, 6 capsules three times per day leaving with 4 capsules with placebo and 2 capsules in the morning and evening with betahistine, betahistine dihydrochloride tablets were over-encapsulated with mannitol and Aerosil as filling material **High dose betahistine:** three times daily 48 mg, 2 capsules 3 times daily, betahistine dihydrochloride tablets were over-encapsulated with mannitol and Aerosil as filling material **Comparator group:** placebo capsules with an identically appearing filled with mannitol and Aerosil but not containing any active ingredient was administered as placebo three times daily **Use of additional interventions:** none reported, change in relevant concomitant drug treatment was registered
Outcomes	• The effect on vertigo was calculated by means of the log-transformed number per 30 day interval in which only changes from baseline were shown comparing the high and low dose betahistine to placebo • The incidence of adverse effects was evaluated at 9 months • The effect on hearing loss was calculated by adjusted mean changes by means of comparing with the placebo group for the high and low dose betahistine group, results were only presented per frequency • The effect on tinnitus was based on the MiniTF questionnaire. Only the adjusted mean change for the placebo was given, whereas, similar to all other outcomes, the results for high dose and lose dose betahistine were based on the difference in comparison to placebo. • The effect on aural fullness was not reported although shown at baseline characteristics table • The incidence of adverse effect was evaluated at 9 months • The effect on disease-specific health-related quality of life was analysed, similar to tinnitus with the adjusted mean change comparing placebo to low and high dose of betahistine
Identification	Sponsorship source: Funding: This study was not industry sponsored. The study was supported by grants from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung (BMBF), support code 01KG0708; sponsor's protocol code no 04T-617). This work was supported by the German Centre for Vertigo and Balance Disorders (DSGZ), University Hospital Munich, Campus Grosshadern, Munich, Germany. The sponsor had no role in the design, management, data collection, analyses, or interpretation of the data or in the writing of the manuscript or the decision to submit for publication. Country: Germany Setting: Tertiary referral centres (14) Comments: None Authors name: Christine Adrion Institution: German centre for Vertigo and Balance Disorders Email: Michael. strupp@med.uni-muenchen.de Address: University Hospital Munich, campus Grosshadern, Munich, Germany

Declaration of interest	Declared no conflict of interest.
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned in a 1:1:1 ratio
Allocation concealment (selection bias)	Low risk	Concealment allocation was performed by an Internet based randomisation schedule stratified by study site, fixed block size was three which was not disclosed during the trial, random list was generated by an investigator with no clinical involvement in the trial
Blinding of participants and personnel (performance bias)	Low risk	Patients, clinicians, core laboratories, trial staff were blind to treatment allocation
Blinding of outcome assessment (detection bias)	Low risk	Patients, clinicians, core laboratories, trial staff were blind to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Reasons for drop-outs were given for all participants.
Selective reporting (reporting bias)	Low risk	All predefined outcomes were analysed
Other bias	Unclear risk	Pre-randomisation attack frequency was not documented although considered as an inclusion criterion. Data was not shown with respect to duration and age at the onset of disease but groups were well balanced based on these characteristics.

Burkin 1967

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 22 participants were allocated to either betahistine or placebo for two weeks and then switch to placebo or betahistine, four week follow-up period **Number completed:** 22 participants, unclear if this was equally balanced across both groups **Participants baseline characteristics:** **Age:** not reported, calculated from raw data 47.1 (SD 5.1) **Gender:** 50% male **Included criteria:** Diagnosed as having Meniere's syndrome, careful examination of each patient and a thorough evaluation of their symptoms; CLASS III **Excluded criteria:** None predefined **Pre-treatment:** Unknown
Interventions	**Intervention group:** betahistine tablets, 16 mg daily, (4 mg 4 times a day) during 2 weeks **Comparator group:** placebo tablets, 4 times a day, during 2 weeks **Use of additional interventions:** none
Outcomes	• Dizziness - present or absent dichotomy • Adverse events
Identification	Sponsorship source: Unknown Country: USA Setting: Department of Otolaryngology Comments: No comment Authors name: Aaron Burkin Institution: Springfield Mercy and Wesson Memorial Hospitals Email: Unavailable Address: Unavailable
Declaration of interest	Not given
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomization was checked with several statistical tests", unclear which statistical tests were used and additional details on methods of randomisation were not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear how blinding of participants and personnel was achieved. Quote: "the study was completely double-blind and neither the investigator nor the patient knew which tablet was the active and which the placebo".
Blinding of outcome assessment (detection bias)	Unclear risk	No details were given
Incomplete outcome data (attrition bias)	Unclear risk	No details were given
Selective reporting (reporting bias)	Low Risk	There was no protocol available. The outcome listed in the material and methods section of the article were all reported in the results section of the article.
Other bias	Unclear risk	No details on statistical analyses were given on how group differences after therapy were calculated and whether these results were statistically significant.

Elia 1966

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 20 participants were allocated to either betahistine (A or C) or placebo (B or D) for two weeks and then switch to placebo or betahistine. This was repeated for two more times. **Number completed:** 16 participants, unclear whether this was equally balanced across both groups **Participants baseline characteristics:** **Age:** not reported **ender:** not reported **Included criteria:** Suffering from intractable vertigo for at least four months. Readily available for examination. Would agree to continue therapy for 8 weeks. Examination every 14 days; CLASS III **Excluded criteria:** None predefined **Pre-treatment:** Unknown
Interventions	**Intervention group:** betahistine tablets, 16 mg daily, (4 mg 4 times a day) during 8 weeks **Comparator group:** placebo tablets, 4 times a day, during 8 weeks **Use of additional interventions:** all medication was discontinued 14 days prior to the patient being included in the study, no medication other than betahistine hydrochloride or placebo was taken by the patient during the period of this study, no information on protocol adherence was reported.
Outcomes	• Subjective change in vertigo based on a 4 point scale (0-3) • Subjective change in tinnitus based on a 4 point scale (0-3) • Subjective change in aural fullness based on a 4 point scale (0-3)
Identification	Sponsorship source: Unknown Country: USA Setting: Washoe Medical Center and St. Mary's Hospital Comments: No comment Authors name: Joseph C. Elia Institution: Washoe Medical Center and St. Mary's Hospital Email: Unavailable Address: 275 Hill St. Reno, Nevada 89504
Declaration of interest	None declared
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on whether the physician was unaware of the sequence generation.
Allocation concealment (selection bias)	Low risk	Uninvolved fifth person generating sequence.
Blinding of participants and personnel (performance bias)	High risk	The same sequence was repeated (A, B, C and D) was used in all patients, could be predicted by the patients, physician and the statistician.
Blinding of outcome assessment (detection bias)	High risk	The same sequence was repeated (A, B, C and D) was used in all patients, could be predicted by the patients, physician and the statistician.
Incomplete outcome data (attrition bias)	High risk	4 out of 20 participants dropped out due to non-compliance to the trial and change of location of the participants.
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcome listed in the material and methods section of the article are all reported in the results section of the article.
Other bias	High risk	No details on how statistical analyses were performed although the authors concluded a positive effect was found for betahistine on Menière's disease.

Frew 1976

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 26 participants were allocated to either betahistine or placebo for eight weeks and then switch to placebo or betahistine. This was repeated for two more times, with a total of 36 weeks. **Number completed:** 22 participants, unclear whether this was equally balanced across both groups. **Participants baseline characteristics:** **Age:** not reported **Gender:** not reported **Included criteria:** diagnosis was based on paroxysmal attacks of rotational vertigo, tinnitus and fluctuating sensorineural deafness; CLASS III **Excluded criteria:** none predefined **Pre-treatment:** unknown
Interventions	**Intervention group:** betahistine tablets, 16 mg daily, (8 mg 2 times a day) during 36 weeks **Comparator group:** placebo tablets, 4 times a day, during 36 weeks **Use of additional interventions:** participants were prescribed placebo 4 weeks prior to the start of the trial.
Outcomes	• Subjective change in vertigo based on a 4 point scale (0-3) • Subjective change in tinnitus based on a 4 point scale (0-3) • Subjective change in aural fullness based on a 4 point scale (0-3)
Identification	Sponsorship source: Unknown Country: Holland Setting: Department of Otorhinolaryngology, Newcastle University Hospitals Group Comments: Philips Duphar's statistician was acknowledged Authors name: I.J.C. Frew Institution: Department of Otorhinolaryngology, Newcastle University Hospitals Group Email: Unknown Address: Department of Otorhinolaryngology, Newcastle University Hospitals Group, no further details on the address was given
Declaration of interest	None declared
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details were given
Allocation concealment (selection bias)	Unclear risk	No details were given
Blinding of participants and personnel (performance bias)	Unclear risk	Physician could break the code if relapse occurred. Unclear if and in how many cases this occurred, blinding cannot be assured.
Blinding of outcome assessment (detection bias)	Unclear risk	No details on blinding of outcome assessment.
Incomplete outcome data (attrition bias)	Unclear risk	Unclear why six patients withdrew, described as "unable to co-operate", no reasons for drop-out were described.
Selective reporting (reporting bias)	High risk	Not all predefined outcomes were reported after assessment by the investigator. Unclear why not all outcomes were summarised by the investigator.
Other bias	High risk	One-sided testing which should be two-sided, standard deviation not reported; high risk of selection bias due to pre-treatment period, allowing the investigator to exclude placebo responders (decreases external validity of study results).

Meyer 1985

Methods	**Study design:** randomised controlled trial **Study grouping:** cross-over
Participants	**Sample size:** **Number randomised:** 40 participants were allocated to either betahistine or placebo for six weeks and then switch to placebo or betahistine. **Number completed:** 40 participants **Participants baseline characteristics:** **Age:** 24-67 years **Gender:** 21 (56) **Included criteria:** Based on patient history, audiometric hearing test results, vestibular testing, radiologic results, neurological and orthopaedic research; CLASS III **Excluded criteria:** Allergic reactions, gastritis, gastric ulcus, hypertonic, liver dysfunction (contra-indication for use of betahistine) **Pre-treatment:** One year before study treatment, during treatment (at 2, 6, 12 weeks) and after one year, outcomes were measured
Interventions	**Intervention group:** Betahistine dihydrochloride, participants were treated with 36 mg daily, 3 times daily 2 tablets **Comparator group:** placebo tablets, 3 times daily two tablets **Use of additional interventions:** none reported
Outcomes	• Subjective change in vertigo based on a 4 point scale (0-3) • Subjective change in tinnitus based on a 4 point scale (0-3) • Subjective change in aural fullness based on a 4 point scale (0-3) • Change in hearing loss was based on the mean three-tone average of thresholds at 0.5 kHz, 1 kHz, 2 kHz
Identification	Sponsorship source: Unknown Country: Germany Setting: HNO-Klinik und Poliklinik Bereich Medizin der Humboldt-Universiat at Berlin Comments: No comment Authors name: E.D. Meyer Institution: HNO-Klinik und Poliklinik Bereich Medizin der Humboldt-Universiat Berlin Email: Unknown Address: Schumannstrasse 20/21 DDR-1040 Berlin
Declaration of interest	None declared
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on sequence generation were given
Allocation concealment (selection bias)	Unclear risk	No details on allocation concealment were given
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear which methods were undertaken to maintain blinding of participant and personnel
Blinding of outcome assessment (detection bias)	Unclear risk	No details on the method of blinding of the outcome assessors were given.
Incomplete outcome data (attrition bias)	High risk	Impaired walking pattern for only 38 patients were reported which implicates missing data although no details on this matter were reported.
Selective reporting (reporting bias)	High risk	Not all outcomes were predefined and details on how these were assessed (tinnitus, gate disturbances and aural fullness)
Other bias	Unclear risk	Inclusion of patients was based on several additional diagnostic test although it remains unclear which diagnostic criteria were mandatory to full fill the diagnosis of Meniere's disease, unclear which statistical analysis were used for each outcome.

Mira 2003

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Sample size:** **Number randomised:** 41 participants were allocated to betahistine, 40 participants were allocated to placebo for 3 months **Number completed:** 81 participants **Participants baseline characteristics:** **Age:** not reported **Gender:** not reported **Included criteria:** Probable or possible MD based on the AAO HNS criteria, Out or in-patient, between 18-65 years old, signed and informed written consent. Withdrawal of interfering concomitant therapies at least 7 days before start of the trial. Normal laboratory documented renal and hepatic functional cooperating by adhering to the scheduled procedure; CLASS II **Excluded criteria:** Concomitant infectious and definite cerebrovascular diseases. Diseases that were not compatible with and were contraindicated by the treatment under study. Concomitant therapy with anti-vertigo drugs. Taking drugs that act on cerebral circulation (antihistamines, antiaggregant, thiazide diuretics, corticosteroids, benzodiazepines), major or surgical condition likely to interfere with the absorption distribution, metabolics or excretion of the drug used in the study, having a terminal disease. **Pre-treatment:** not reported
Interventions	**Intervention group:** betahistine dihydrochloride, participants were treated with 32 mg daily, 16 mg 2 times per day **Comparator group:** placebo tablets, 2 times daily 2 tablets **Use of additional interventions:** none reported
Outcomes	• The effect on vertigo was reported by means of the mean number of vertigo attacks per month • The incidence of significant adverse effects at 3 months • Subjective change in tinnitus based on a 5 point scale (0-4) • Subjective change in aural fullness based on a 5 point scale (0-4), data was not specified for aural fullness • The incidence of other adverse effects at 3 months • The disease-specific health-related quality of life, based on a 3 point scale

Identification	**Sponsorship source:** Grant from Grunethal-Formenti, Milan Italy **Country:** Italy **Setting:** Multicentre **Comments:** No comment **Authors name:** Eugenio Mira **Institution:** University of Pavia **Email:** e.mira@smatteo.pv.it **Address:** Not given
Declaration of interest	None declared
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear who made and kept the randomisation list
Allocation concealment (selection bias)	Unclear risk	No details on the allocation concealment were given
Blinding of participants and personnel (performance bias)	Low risk	Attempts made to assure blinding
Blinding of outcome assessment (detection bias)	Low risk	Attempts made to assure blinding
Incomplete outcome data (attrition bias)	High risk	Not balanced across groups and related to outcome
Selective reporting (reporting bias)	Low risk	Results of all outcomes described
Other bias	High risk	No references on the determination of the sample size calculation were available; improvement of associated symptoms including tinnitus, fullness of the ear, nausea and vomiting are summarised in one figure whereas it remains unknown how calculations were performed, unknown if complete data was available

Okamato 1968

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 40 participants were allocated to betahistine or placebo **Number completed:** 36 participants, 2 drop outs in the betahistine and 2 drop outs placebo group **Participants baseline characteristics:** **Age:** not reported **Gender:** 13 males (36%) **Included criteria:** diagnosed as Meniere's disease from their anamnesis (past history), and through hearing examination and vestibular function examination. Patients had to suffer from accompanying paroxysmal vertigo, deafness and tinnitus; CLASS III **Excluded criteria:** not defined **Pre-treatment:** not reported
Interventions	**Intervention group:** betahistine dihydrochloride, 36 mg per day, 6 tablets per day, 2 times 3 tablets daily for two weeks **Comparator group:** 6 tablets per day. 2 times 3 tablets daily prepared identically in appearance, taste and smell for two weeks **Use of additional interventions:** none reported
Outcomes	• Subjective change in vertigo based on a 3 point scale (0-2) • Subjective change in tinnitus based on a 3 point scale (0-2) • Subjective change in hearing loss based on a 3 point scale (0-2) • Change in the incidence of other adverse effects based on a 3 point scale (0-2)
Identification	**Sponsorship source:** Eisai Co., Ltd. **Country:** Tokyo **Setting:** The 2nd Tokyo National Hospital **Comments:** **Authors name:** Ken Okamoto **Institution:** The 2nd Tokyo National Hospital **Email:** y-hayakawa@hhc.eisai.co.jp **Address:** Unknown
Declaration of interest	None declared
Notes	Medication supplied by Eisai Co; unclear what the role of the subsidising party was

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generations (selection bias)	Low risk	Drug bottles were labelled with a random serial number on a layout
Allocation concealment (selection bias)	Low risk	The table of random numbers was created by an independent third party from the medical institution
Blinding of participants and personnel (performance bias)	Low risk	In the discussion it was claimed that both patients and doctors were unaware of the drug they had been given
Blinding of outcome assessment (detection bias)	Unclear risk	No methods on the blinding of outcome assessors were provided
Incomplete outcome data (attrition bias)	High risk	4 drop outs not due to adverse effect of the drug, unknown
Selective reporting (reporting bias)	Low risk	There was no protocol available, the outcomes listed in the method section of the article were all reported in the results section
Other bias	High risk	Medication supplied by Eisai Co; unclear what the role of the subsidising party was

Ricci 1987

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 10 participants were allocated to betahistine or placebo evaluated after 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment **Number completed:** 10 participants **Participants baseline characteristics:** **Age:** betahistine 36.4 years (SD 2.2); placebo 37.0 years (SD 5.4) **Gender:** 6 males (60%) **Included criteria:** Meniere's disease patients; CLASS III **Excluded criteria:** Hypertensivity against betahistine, peptic ulcer, gastroduodenitis, pheochromocytoma, asthma, grave asthenia, arterial hypertension, renal or hepatic insufficiency **Pre-treatment:** not reported
Interventions	**Intervention group:** betahistine hydrochloride 24 mg per day, 3 times a day at a meal, 16 drops, equal to 8 mg of active ingredient, for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment **Comparator group:** not reported **Use of additional interventions:** during the study, concomitant using of anti-vertigo drugs, drugs acting on the cerebral circulation, anti-histamines and histamines mimetics were prohibited
Outcomes	• Subjective change in vertigo based on a 3 point scale (1-3) • Change in objective hearing loss classified based on the mean hearing thresholds of 0.5, 1 kHz, 2 kHz classified according to ANSI (6 classes) • Subjective change in tinnitus based on a 7 point scale (0-6) • Subjective change in aural fullness based on a 7 point scale (0-6)
Identification	**Sponsorship source:** Not reported **Country:** Italy **Setting:** University of Verona **Comments:** **Authors name:** V. Ricci **Institution:** Universita degli Studi di Verona **Email:** Not available **Address:** Clinica Otorinolaringoiastica; Universita di Verona, 37100 Verona
Declaration of interest	None declared
Notes	

Risk of bias

Bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assigned to the treatment groups based on a randomisation list
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was available
Blinding of outcome assessment (detection bias)	Unclear risk	No information was available on blinding of the outcome assessors
Incomplete outcome data (attrition bias)	Unclear risk	No drop outs or lost to follow-up was reported
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcome listed in the material and methods section of the article are all reported in the results section of the article
Other bias	Unclear risk	No information was available regarding the performed statistical analyses

Salami 1984

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	**Sample size:** **Number randomised:** 15 participants were allocated to betahistine, 15 participants were allocated to the placebo who were evaluated after 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment during 6 weeks **Number completed:** 30 participants **Participants baseline characteristics:** **Age:** betahistine 49.6 years (SD 4); placebo 42.7 years (SD 3.5) **Gender:** 17 males (56%) **Included criteria:** Vascular of neurovascular Meniere's syndrome, criteria for diagnosis were not stated; CLASS III **Excluded criteria:** Patients with vertigo of extra-vestibular origin (visual, proprioceptive mental), patients with a history of peptic ulcer, pheochromocytoma, asthma, ictus cerebri (cerebral shock, exhaustion (grave asthenia)), arterial hypertension, patients with hepatic or renal insufficiency, patients with alteration of gonad or thyroid function, those exposed to prolonged treatments with drugs that are potentially ototoxic (quinine, salicylates, aminoglycoside, furosemide) those regularly using narcotics, lactating or pregnant women, and those with a proven hypersensitivity to betahistine hydrochloride. **Pre-treatment:** not reported
Interventions	**Intervention group:** betahistine hydrochloride 24 mg per day, 3 times a day at a meal, 16 drops, equal to 8 mg of active ingredient, for a period equivalent to 10 times the mean duration of the interval between attacks of vertigo reported prior to treatment. **Comparator group:** not reported **Use of additional interventions:** during the study, concomitant using of anti-vertigo drugs, drugs acting on the cerebral circulation, anti-histamines and histamines mimetics were prohibited
Outcomes	Subjective change in vertigo based on a 4 point scale (0-3) Objective change in hearing loss classified based on the mean hearing thresholds of 0.5, 1 kHz, 2 and 3 kHz Subjective change in tinnitus based on a 7 point scale (0-6) Subjective change in aural fullness based on a 7 point scale (0-6)

Identification	**Sponsorship source:** Not applicable **Country:** Italy **Setting:** Outpatient department Otorhinolaryngology **Comments:** **Authors name:** A. Salami **Institution:** Clinica Otorinolaringoiatrica B dell'Univerisita **Email:** Not available **Address:** Viale Benedetto XV 16132 Genova
Declaration of interest	None declared.
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on random sequence generation was available
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participant and personnel was available
Blinding of outcome assessment (detection bias)	Unclear risk	No information on blinding of outcome assessors was available
Incomplete outcome data (attrition bias)	Unclear risk	No lost to follow-up or drop outs were reported but it remains if all patients were evaluated during the analysis for all outcomes
Selective reporting (reporting bias)	Low risk	There is no protocol available. The outcome listed in the material and methods section of the article are all reported in the results section of the article
Other bias	Unclear risk	Unclear how statistical analysis were performed

Schmidt 1992

Methods	**Study design:** randomised controlled trial **Study grouping:** crossover
Participants	**Sample size:** **Number randomised:** 40 participants were allocated to either to betahistine or placebo who switch from therapy after a period of 16 weeks, outcomes were measured every month with a total follow-up period 33 weeks **Number completed:** 35 participants **Participants baseline characteristics:** **Age:** betahistine 49.5 years (SD 10.1); placebo 49.1 years (SD 7.5) **Gender:** 24 males (82%) **Unilateral versus bilateral disease**: 27 (77%) **Included criteria:** Complete MD, unilateral or bilateral, according to the Utrecht working definition, i.e.: cochlear hearing loss, (history of) tinnitus, attacks of vertigo, exclusion of all other diseases that could account for the symptoms Exacerbation of symptoms during the previous month, for which patients sought medical help; CLASS II **Excluded criteria:** - Patients with other otological or general diseases, patients who had undergone surgical treatment for MD, patients who used medication that was likely to influence MD, it this medications had to be continued, patients who were using betahistine dihydrochloride, patients who had experienced side-effect of betahistine dihydrochloride - Patients with an apparent infection of the middle or the inner ear, with peptic ulcer, bronchial asthma or pheochromocytoma, who were pregnant, suffering from liver or kidney insufficiency, brain tumour, recent head trauma, Parkinson's disease, epilepsy, multiple sclerosis or any other generalised disease, operated upon because of MD, using antihistamines, anti-vertiginous drugs, vasodilators, psychotropic drugs or tranquillizers, in case use of these drugs could not be stopped, who had been using betahistine dihydrochloride 3 times 16 mg daily or more for at least the previous three months, who had experienced side effect during previous use of betahistine dihydrochloride **Pre-treatment:** One week with no use of any medication to create a wash-out effect.
Interventions	**Intervention group:** betahistine dihydrochloride 24 mg 3 times per day, total 72 mg per day with a sustained formula **Comparator group:** placebo capsules with an identical appearing 3 times per day **Use of additional interventions:** not reported

Outcomes	• Vertigo was noted as imbalance based on number of attacks, multiplying the number by 1, 4 or 9 for a mild, moderate or severe attack respectively • The incidence of adverse effects • Objective change in hearing loss classified based on the mean hearing thresholds of 0.25 to 2 kHz • Subjective change in tinnitus based on a 4 point scale (none, mild, moderate, severe) • Subjective change in aural fullness based on a 4 point scale (none, mild, moderate, severe) • The incidence of other adverse effects
Identification	**Sponsorship source:** Duphar Nederland B.V. **Country:** The Netherlands **Setting:** Outpatient Clinic of Otorhinolaryngology Head and Neck Surgery University Medical Centre Utrecht **Comments:** **Authors name:** J. Schmidt **Institution:** Otorhinolaryngology Head and Neck Surgery University Medical Centre Utrecht **Email:** Not available **Address:** Not available
Declaration of interest	None declared
Notes	

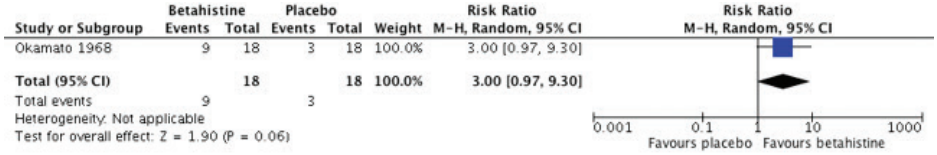
Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generations (selection bias)	Unclear risk	No details on random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment was available.
Blinding of participants and personnel (performance bias)	Unclear risk	No information on blinding of participants and personnel was available.
Blinding of outcome assessment (detection bias)	Unclear risk	No information on blinding of outcome assessment was available.
Incomplete outcome data (attrition bias)	Low risk	Reasons for drop outs described, including an intention to treat analysis
Selective reporting (reporting bias)	Low risk	There was no protocol available. The outcomes listed in the material and methods section of the article are all reported in the results section of the article.
Other bias	High risk	Intention to treat analysis not applied because one patient crossed over due to side effects earlier than the protocol described but the data were analysed per protocol. Follow-up data from drop outs was not accounted for.

Data and analyses

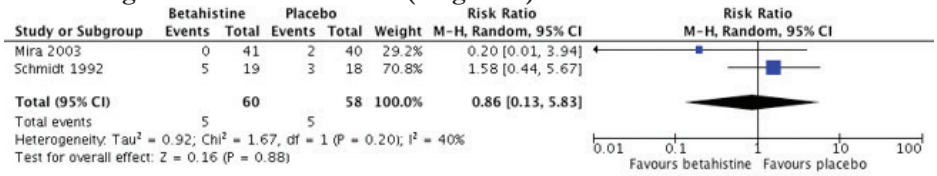
1 Betahistine versus placebo

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Vertigo considering together intensity, frequency and duration of symptoms (short-term)	1	36	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.97, 9.30]
1.2 Vertigo considering together intensity, frequency and duration of symptoms (long term)	3	259	Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Significant adverse effects (long term)	2	118	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.13,5.83]
1.4 Hearing loss (short term)	1	36	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.34, 26.19]
1.5 Hearing loss (long term)	1	10	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.15, 59.89]
1.6 Hearing loss (long term)	1	35	Mean Difference (IV, Random, 95% CI)	10.10 [-0.97, 21.17]
1.7 Tinnitus (short term)	1	36	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.84, 8.46]
1.8 Tinnitus (long term)	1	10	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.71, 1.41]
1.9 Tinnitus (long term)	1	144	Std. Mean Difference (IV, Random, 95% CI)	-016 [-0.48, 0.17]
1.10 Other adverse effects (long term)	1	36	Std. Mean Difference (IV, Random, 95% CI)	1.67 [0.47, 5.96]
1.11 Other adverse effects (long term)	3	265	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.21, 5.49]
1.12 Well-being and disease-specific quality of life (long term)	1	144	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.25, 0.40]

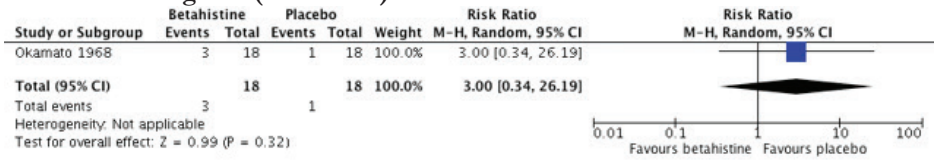
1.1 Vertigo considering together intensity, frequency and duration of symptoms (short-term)



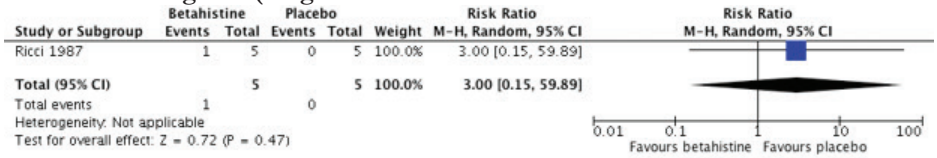
1.3 Significant adverse effects (long term)



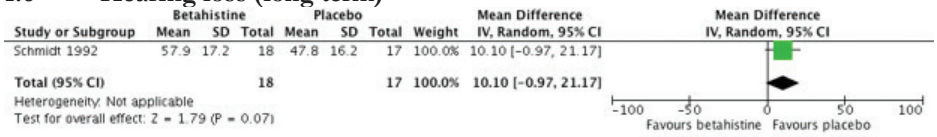
1.4 Hearing loss (short term)



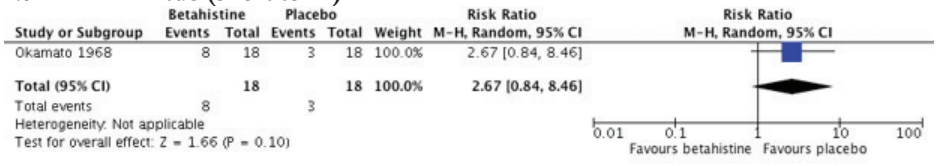
1.5 Hearing loss (long term



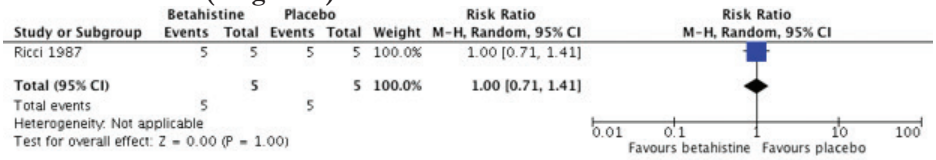
1.6 Hearing loss (long term)



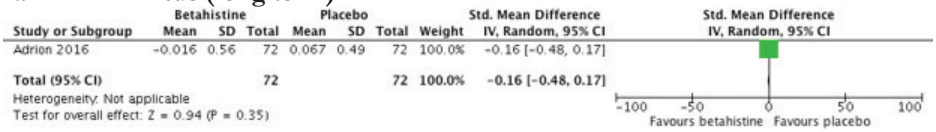
1.7 Tinnitus (short term)



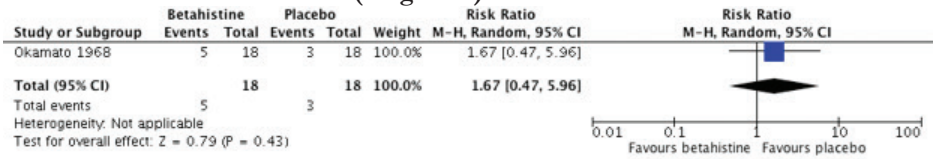
1.8 Tinnitus (long term)



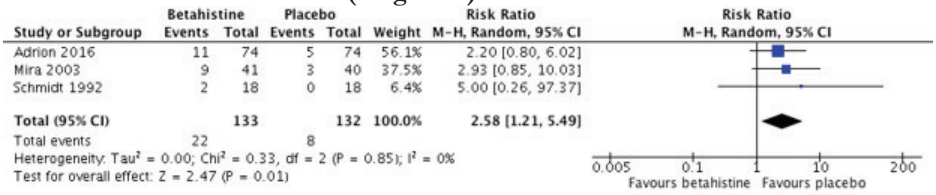
1.9 Tinnitus (long term)



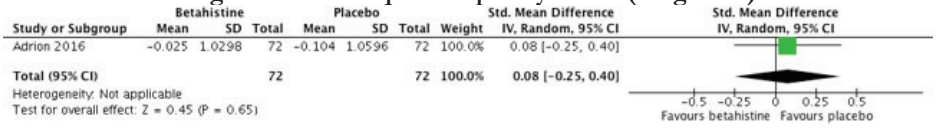
1.10 Other adverse effects (long term)



1.11 Other adverse effects (long term)



1.12 Well-being and disease-specific quality of life (long term)



APPENDICES

Appendix 1. Diagnostic criteria defined for Menière's disease by the American Academy of Otolaryngology – Head and Neck Surgery in 1995

TABLE I

AAO-HNS 1995 CRITERIA FOR MÉNIÈRE'S DISEASE

Certain Ménière's disease
– Definitive Ménière's disease
– Histopathological confirmation
Definite Ménière's disease
– ≥2 definitive spontaneous vertigo episodes of 20+ mins duration
– Audiometrically documented hearing loss on 1 occasion
– Tinnitus or aural fullness in treated ear
– Other causes excluded
Probable Ménière's disease
– 1 definitive spontaneous vertigo episode of 20+ mins duration
– Audiometrically documented hearing loss on 1 occasion
– Tinnitus or aural fullness in treated ear
– Other causes excluded
Possible Ménière's disease
– Episodic vertigo of Ménière's disease type, without hearing loss, or,
– Fluctuating or fixed SNHL, with disequilibrium but with no definitive episodes
– Other causes excluded

AAO-HNS = American Academy of Otolaryngology-Head and Neck Surgery; mins = minutes; SNHL = sensorineural hearing loss

Appendix 2. AAO-HNS outcome measures

The AAO-HNS Committee on Hearing and Equilibrium proposed the "control of vertigo" as a main objective outcome measure when assessing therapy in Ménière's disease. The number of attacks six months prior to treatment is compared to the number of attacks in the period between 18 and 24 months following treatment. The resulting number indicates the extent of "control of vertigo". The AAO-HNS further divides the control of vertigo into classes, where Class A (CoV = 100% control) is complete control and class B (CoV 99 to 60%%) is substantial control. They recommend a period of at least two years of follow-up in order to assess fully the effect of the intervention. We will also consider studies with shorter periods of follow-up for this review (AAO-HNS 1995).

Appendix 3. Tinnitus Handicap Inventory

The purpose of this questionnaire is to identify difficulties that you may be experiencing because of your tinnitus. Please answer every question. Please do not skip any questions.

1. Because of your tinnitus, is it difficult for you to concentrate?	Yes	Sometimes	No
2. Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	Sometimes	No
3. Does your tinnitus make you angry?	Yes	Sometimes	No
4. Does your tinnitus make you feel confused?	Yes	Sometimes	No
5. Because of your tinnitus, do you feel desperate?	Yes	Sometimes	No
6. Do you complain a great deal about your tinnitus?	Yes	Sometimes	No
7. Because of your tinnitus, do you have trouble falling to sleep at night?	Yes	Sometimes	No
Does your tinnitus interfere with your ability to enjoy your social activities (such as going out to dinner, to the movies)?	Yes	Sometimes	No
10. Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
10. Because of your tinnitus, do you feel frustrated?	Yes	Sometimes	No
11. Because of your tinnitus, do you feel that you have a terrible disease?	Yes	Sometimes	No
12. Does your tinnitus make it difficult for you to enjoy life?	Yes	Sometimes	No
13. Does your tinnitus interfere with your job or household responsibilities?	Yes	Sometimes	No
14. Because of your tinnitus, do you find that you are often irritable?	Yes	Sometimes	No
15. Because of your tinnitus, is it difficult for you to read?	Yes	Sometimes	No
16. Does your tinnitus make you upset?	Yes	Sometimes	No
17. Do you feel that your tinnitus problem has placed stress on your relationships with members of your family and friends?	Yes	Sometimes	No
18. Do you find it difficult to focus your attention away from your tinnitus and on other things?	Yes	Sometimes	No
19. Do you feel that you have no control over your tinnitus?	Yes	Sometimes	No
20. Because of your tinnitus, do you often feel tired?	Yes	Sometimes	No
21. Because of your tinnitus, do you feel depressed?	Yes	Sometimes	No
22. Does your tinnitus make you feel anxious?	Yes	Sometimes	No
23. Do you feel that you can no longer cope with your tinnitus?	Yes	Sometimes	No
24. Does your tinnitus get worse when you are under stress?	Yes	Sometimes	No
25. Does your tinnitus make you feel insecure?	Yes	Sometimes	No

For interpretation of the THI score

Total score = (number or 'Yes' responses x4) + (number of 'Sometimes' responses x2) = …

Grade of handicap due to tinnitus

Grade	Score	Description
1	0 to 16	Slight: only heard in quiet environment, very easily masked. No interference with sleep or daily activities.
2	18 to 36	Mild: easily masked by environmental sounds and easily forgotten with activities. May occasionally interfere with sleep but not daily activities.
3	38 to 56	Moderate: may be noticed, even in the presence of background or environmental noise, although daily activities may still be performed.
4	58 to 76	Severe: almost always heard, rarely, if ever, masked. Leads to disturbed sleep pattern and can interfere with ability to carry out normal daily activities. Quiet activities affected adversely.
5	78 to 100	Catastrophic: always heard, disturbed sleep patterns, difficulty with any activity

Newman CW, Jacobson., Spitzer, JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg,* 1996; 122:143-8

Appendix 4. Functional Level Scale

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

Appendix 5. Dizziness Handicap Inventory

P1. Does looking up increase your problem?	o Yes o Sometimes o No
E2. Because of your problem, do you feel frustrated?	o Yes o Sometimes o No
F3. Because of your problem, do you restrict your travel for business or recreation?	o Yes o Sometimes o No
P4. Does walking down the aisle of a supermarket increase your problems?	o Yes o Sometimes o No
F5. Because of your problem, do you have difficulty getting into or out of bed?	o Yes o Sometimes o No
F6. Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to the movies, dancing, or going to parties?	o Yes o Sometimes o No
F7. Because of your problem, do you have difficulty reading?	o Yes o Sometimes o No
P8. Does performing more ambitious activities such as sports, dancing, household chores (sweeping or putting dishes away) increase your problems?	o Yes o Sometimes o No
E9. Because of your problem, are you afraid to leave your home without having without having someone accompany you?	o Yes o Sometimes o No
E10. Because of your problem have you been embarrassed in front of others?	o Yes o Sometimes o No
P11. Do quick movements of your head increase your problem?	o Yes o Sometimes o No
F12. Because of your problem, do you avoid heights?	o Yes o Sometimes o No
P13. Does turning over in bed increase your problem?	o Yes o Sometimes o No
F14. Because of your problem, is it difficult for you to do strenuous homework or yard work?	o Yes o Sometimes o No

E15. Because of your problem, are you afraid people may think you are intoxicated?	o Yes o Sometimes o No
F16. Because of your problem, is it difficult for you to go for a walk by yourself?	o Yes o Sometimes o No
P17. Does walking down a sidewalk increase your problem?	o Yes o Sometimes o No
E18.Because of your problem, is it difficult for you to concentrate	o Yes o Sometimes o No
F19. Because of your problem, is it difficult for you to walk around your house in the dark?	o Yes o Sometimes o No
E20. Because of your problem, are you afraid to stay home alone?	o Yes o Sometimes o No
E21. Because of your problem, do you feel handicapped?	o Yes o Sometimes o No
E22. Has the problem placed stress on your relationships with members of your family or friends?	o Yes o Sometimes o No
E23. Because of your problem, are you depressed?	o Yes o Sometimes o No
F24. Does your problem interfere with your job or household responsibilities?	o Yes o Sometimes o No
P25. Does bending over increase your problem?	o Yes o Sometimes o No

The patient is asked to answer each question as it pertains to dizziness or unsteadiness problems, specifically considering their condition during the last month. Questions are designed to incorporate functional (F), physical (P), and emotional (E) impacts on disability. To each item, the following scores can be assigned: No=0; Sometimes=2; Yes=4. Scores greater than 10 points should be referred to balance specialists for further evaluation; 16-34 Points (mild handicap); 36-52 Points (moderate handicap); 54+ Points (severe handicap)

Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1990;116: 424-427

Appendix 6. Search strategies

Central	1 MESH DESCRIPTOR Meniere Disease EXPLODE ALL AND CENTRAL:TARGET 2 (meniere* OR meniere's OR menieres):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 4 #1 OR #2 OR #3 5 MESH DESCRIPTOR Betahistine EXPLODE ALL AND CENTRAL:TARGET 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 7 #5 OR #6 8 #4 AND #7 9 MESH DESCRIPTOR Meniere Disease EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET 10 #8 OR #9
Medline (Ovid)	1 exp Endolymphatic Hydrops/ 2 (meniere* or meniere's or menieres).ab,ti. 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).ab,ti. 4 1 or 2 or 3 5 exp Betahistine/ 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL).ab,ti. 7 5 or 6 8 4 and 7 9 randomized controlled trial.pt 10 controlled clinical trial.pt. 11 randomized.ab. 12 placebo.ab. 13 drug therapy.fs. 14 randomly.ab. 15 trial.ab. 16 groups.ab. 17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18 exp animals/ not humans.sh. 19 17 not 18 20 8 and 19

Embase (Ovid)	1 exp Meniere disease/ 2 (meniere* or meniere's or menieres).ab,ti. 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).ab,ti. 4 1 or 2 or 3 5 exp betahistine/ 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL).ab,ti. 7 5 or 6 8 4 and 7 9 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 10 (control* adj group*).tw. 11 (trial* and (control* or comparative)).tw. 12 ((blind* or mask*) and (single or double or triple or treble)).tw. 13 (treatment adj arm*).tw. 14 (control* adj group*).tw. 15 (phase adj (III or three)).tw. 16 (versus or vs).tw. 17 rct.tw. 18 crossover procedure/ 19 double blind procedure/ 20 single blind procedure/ 21 randomization/ 22 placebo/ 23 exp clinical trial/ 24 parallel design/ 25 Latin square design/ 26 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 28 exp human 29 27 not 28 30 26 not 29 31 8 and 30

Web of Science (Web of Knowledge)	1 exp Meniere disease/ 2 (meniere* or meniere's or menieres).ab,ti. 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)).ab,ti. 4 1 or 2 or 3 5 exp betahistine 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL).ab,ti. 7 5 or 6 8 4 and 7 9 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 10 (control* adj group*).tw. 11 (trial* and (control* or comparative)).tw. 12 ((blind* or mask*) and (single or double or triple or treble)).tw. 13 (treatment adj arm*).tw. 14 (control* adj group*).tw. 15 (phase adj (III or three)).tw 16 (versus or vs).tw. 17 rct.tw. 18 crossover procedure/ 19 double blind procedure/ 20 single blind procedure/ 21 randomization/ 22 placebo/ 23 exp clinical trial/ 24 parallel design/ 25 Latin square design/ 26 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 28 exp human/ 29 27 not 28 30 26 not 29 31 8 and 30

Register	1 MESH DESCRIPTOR Meniere Disease EXPLODE ALL AND INREGISTER 2 (meniere* OR meniere's OR menieres):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 3 ((ENDOLYMPHATIC and HYDROPS) or (LABYRINTH and HYDROPS) or (LABYRINTH and SYNDROME) or (aural and vertigo) or (labyrinth and vertigo) or (cochlea and hydrops)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 4 #1 OR #2 OR #3 5 MESH DESCRIPTOR Betahistine EXPLODE ALL AND INREGISTER 6 (BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 7 #5 OR #6 8 #4 AND #7 9 MESH DESCRIPTOR Meniere Disease EXPLODE ALL WITH QUALIFIER DT AND INREGISTER 10 #8 OR #9
Clinicaltrials.gov	(meniere's OR menieres OR (ENDOLYMPHATIC AND HYDROPS) OR (LABYRINTH AND HYDROPS) OR (LABYRINTH AND SYNDROME) OR (aural AND vertigo) OR (labyrinth AND vertigo) OR (cochlea AND hydrops)) AND (BETAHISTINE OR BETAHISTINA OR BETAISTINA OR SERC OR AEQUAMEN OR BETASERC OR BETASERK OR BEATSERKA OR EXTOVYL OR FIDIUM OR LECTIL OR LOBIONE OR MEGINALISK OR MELOPAT OR MENIACE OR MERISLON OR MICROSER OR RIBRAIN OR VASOMOTAL) via Cochrane Regiter of Studies 1 BETAHISTIN* or BETAISTINA or SERC or AEQUAMEN or BETASERC or BETASERK or BEATSERKA or EXTOVYL or FIDIUM or LECTIL or LOBIONE or MEGINALISK or MELOPAT or MENIACE or MERISLON or MICROSER or RIBRAIN or VASOMOTAL AND INSEGMENT 2 nct* AND INSEGMENT 3 #1 AND #2
ICTRP	meniere's AND betahistin* OR meniere* AND betahistin* OR meniere's AND serc OR meniere* AND serc OR meniere's AND betaserc OR meniere* AND betaserc

LILACS	Controlled Clinical Trials (TW:meniere's OR TW:menieres OR (TW:ENDOLYMPHATIC AND TW:HYDROPS) OR (TW:LABYRINTH AND TW:HYDROPS) OR (TW:LABYRINTH AND TW:SYNDROME) OR (TW:aural AND TW:vertigo) OR (TW:labyrinth AND TW:vertigo) OR (TW:cochlea AND TW:hydrops)) AND (TW:BETAHISTINE OR TW:BETAHISTINA OR TW:BETAISTINA OR TW:SERC OR TW:AEQUAMEN OR TW:BETASERC OR TW:BETASERK OR TW:BEATSERKA OR TW:EXTOVYL OR TW:FIDIUM OR TW:LECTIL OR TW:LOBIONE OR TW:MEGINALISK OR TW:MELOPAT OR TW:MENIACE OR TW:MERISLON OR TW:MICROSER OR TW:RIBRAIN OR TW:VASOMOTAL OR TW:beta-Histina)

Appendix 7. Staging of definite and certain Menière's disease

Stage	Four-tone average (dB)
1	**≤25**
2	**26 to 40**
3	**41 to 70**
4	**>70**

Staging is based on the four-tone average (arithmetic mean rounded to the nearest whole number) of the pure-tone thresholds at 0.5 kHz, 1 kHz, 2 kHz and 3 kHz of the worst audiogram during the interval six months before treatment. This is the same audiogram that is used as the baseline evaluation to determine hearing outcome from treatment. Staging should be applied only to cases of definite or certain Menière's disease.

Contributions of authors

All authors were involved in the drafting of the protocol.

Babette van Esch: BE selected and obtained studies, extracted data and assessed risk of bias. BE entered data into RevMan 5 and carried out and interpreted the analyses. BE drafted the final review and has responsibility for updating and maintaining the review.

Hester J Van der Zaag-Loonen: HZ selected studies, extracted data, assessed risk of bias and helped interpret the analyses. HZ provided advice throughout the analyses and drafted the final review.

Tjasse Bruintjes: TB provided advice and drafted the final review.

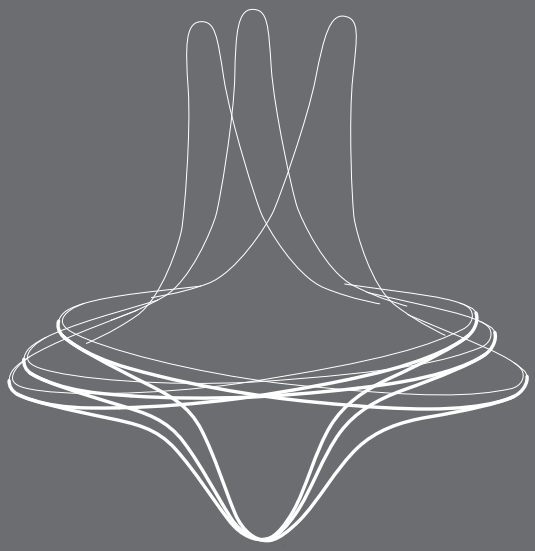
Louisa Murdin: LM provided advice and drafted the final review.

Adrian James: AJ provided advice and drafted the final review.

Peter Paul van Benthem: PB initiated the revision of the review, provided advice and drafted the final review.

Declarations of interest

Babette van Esch: none known.
Tjasse Bruintjes: none known.
Hester J Van der Zaag-Loonen: none known.
Louisa Murdin: none known.
Adrian James: none known.
Peter Paul van Benthem: none known.



10

INTERVENTIONS FOR MENIÈRE'S DISEASE: PROTOCOL FOR AN UMBRELLA SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: The large number of treatment modalities for patients diagnosed with Menière's disease (MD) complicates the selection of the best available treatment as the comparative efficacy of these interventions is not clear. We aim to identify the treatment or treatments with the highest efficacy of current pharmacological and non-pharmacological treatments for MD.

Method and analysis: We will identify all available systematic reviews on the treatment of MD. An online database search will be conducted in association with the UK Cochrane Centre, particularly the Ear, Nose and Throat Group. We will screen the systematic reviews for eligible randomised controlled trials (RCTs) to execute a network meta-analysis. In addition, online databases will be checked for eligible RCTs on treatments that were published after the latest systematic search was conducted. The characteristics of each RCT will be summarised, including the general design, the participants, the interventions, the outcome measurements, the duration of therapy and adverse events. The risk of bias will be assessed by means of the Cochrane Collaboration's risk of bias tool. The included studies will be assessed for methodological and statistical heterogeneity, the latter will be quantified by means of the I^2 statistic. The primary outcome will be the efficacy of treatment in terms of control of vertigo attacks. Secondary outcome measures will be the loss or improvement of hearing, severity of vertigo attacks and tinnitus, perception of aural fullness, quality of life and the incidence of adverse events and complications.

Ethics and dissemination: Formal ethical approval is not required, as primary data will not be collected. The review will be disseminated in peer-reviewed publications and conference presentations.

Trial registration number: PROSPERO CRD42015024243

INTRODUCTION

Menière's disease (MD) is an inner ear disorder characterised by incapacitating attacks of vertigo accompanied by nausea and vomiting, fluctuating sensorineural hearing loss as well as tinnitus and/or aural fullness. Even though the disease was first described in 1861 by Prosper Menière [1], there are still many unanswered questions regarding the pathophysiology of the disease. Furthermore, a definite and effective evidence-based treatment has not been established yet.

The main aim of the treatment in MD is to reduce the frequency and intensity of the vertigo attacks and at the same time to preserve hearing and vestibular function [2].Psychological suffering and reduced quality of life are linked to MD, as disabling vertigo attacks can occur without warning [3,4]. Therefore, an effective prophylactic treatment is necessary to improve the quality of life of MD patients. Current pharmacological treatment options include betahistine, diuretics, oral steroids or intratympanic application of gentamicin or corticosteroids [5]. However, evidence in terms of reducing vertigo complaints has never been conclusive [6.7,8], except for intratympanic gentamicin treatment [9]. Non-pharmacological treatment options include positive pressure therapy (the Meniett device), ablative surgery such as vestibular nerve section, labyrinthectomy and endolymphatic sac surgery [2,5,10]. As for the pharmacological treatment modalities, high quality evidence is also lacking for non-pharmacological therapies [10,11]. Since so many treatments exist without conclusive results, it may be hard for patients and their physicians to select the best available treatment. To date, no umbrella systematic review exists that summarises the body of evidence and states implications for clinical practice.

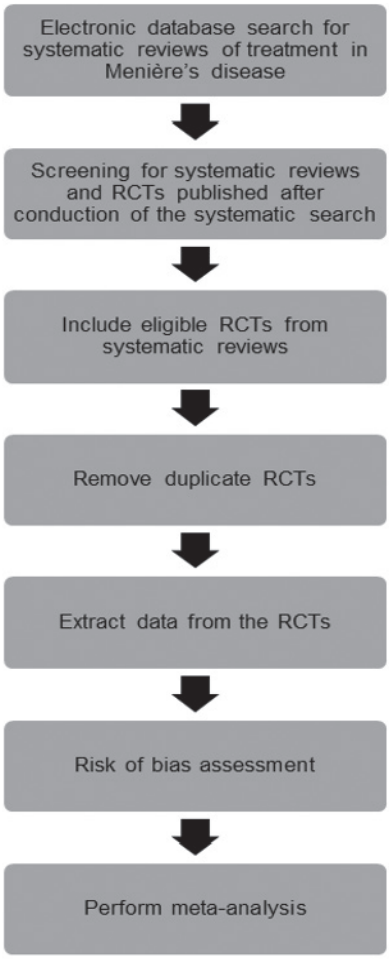
Objective

The present study aims to systematically summarise the interventions for MD, aiming to identify the treatment or treatments with the highest efficacy and to identify areas for future valuable research.

METHODS

Study design

A large number of pharmacological and non-pharmacological trials for the treatment of MD exist. We will conduct an umbrella systematic review of published RCTs of those interventions that have been systematically reviewed. From here we seek to evaluate the efficacy of therapy for MD. The current review has been registered at PROSPERO CRD42015024243. The steps throughout the conduct of the umbrella systematic review are shown in **Figure 1**. This protocol is reported in line with PRISMA-P [12].



60.

Figure 1. Flowchart of the umbrella systematic review (RCTs, randomised controlled trials).

Eligibility criteria

Types of studies

The following study designs will be eligible for inclusion:

- Systematic review (SR) or meta-analysis (MA)
- RCTs or placebo controlled trials

We will screen interventional SRs for eligible RCTs and data from these RCTs will be extracted to execute a network meta-analysis. In addition, online databases will be checked for eligible RCTs on treatments that were systematically reviewed yet published subsequent to the date the latest systematic search was conducted.

Types of participants

Due to the great variability in the clinical presentation of MD, the disorder is not always easy to diagnose. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines to facilitate the diagnosis of MD and to improve comparability of outcome measures when performing trials on patients with MD [13]. In 2015, a new set of diagnostic criteria were jointly formulated by the Classification Committee of the Bárány Society, the Japan Society of Equilibrium Research, the European Academy of Otology and Neurotology, the AAO-HNS and the Korean Balance Society in order to develop an international consensus on diagnostic criteria for MD in order to facilitate future collaborative studies [14]. However, as these international diagnostic criteria were only published recently and previous research widely used the AAO-HNS 1995 diagnostic guidelines, the latter set of criteria will be used to identify 'definite' Ménière's disease patients in the current review.

Types of intervention

We will include RCTs analysing the efficacy of any treatment modality in MD. Treatment modalities that have not been assessed systematically will not be included in the umbrella systematic review. As the natural course of MD has a waning pattern, time should be regarded as a therapeutic factor when analysing the efficacy of a therapeutic intervention. Therefore, a study design including a placebo arm is essential to account for the illusion of therapeutic efficacy. Pharmacological trials with a placebo group will be included; trials comparing different pharmacological treatments without a placebo will be excluded. We will include trials that investigated non-pharmacological interventions and compared the efficacy of the intervention with a sham intervention group, a placebo pill group or a placebo control group.

Types of outcome measures

Outcomes as defined by the AAO-HNS guidelines of 1995 [13] will be included in this umbrella systematic review. The following outcomes are listed as primary and secondary outcomes:

Primary outcomes

1. The main outcome of efficacy will be the control of vertigo as defined by the AAO-HNS guidelines of 1995 [13]. The number of vertigo attacks in the interval after treatment (Y) is divided by the number of vertigo spells six months prior to treatment (X) and multiplied by 100. The resulting number indicates the extent of 'control of vertigo'. The AAO-HNS further divides the control of vertigo into classes, where Class A (CoV =0) represents a complete control of vertigo and class B (CoV up to 40%) represents a substantial control of vertigo. Assessment of control of vertigo by

any other outcome measures (e.g. mean frequency of vertigo attacks at baseline and at the final assessment) will also be accepted.

Secondary outcomes

Secondary outcome measures will be:

1. Hearing (based on the pure-tone audiometry).
2. The severity of vertigo attacks (assessed by means of a standardised method (e.g. the Visual Analogue Scale (VAS) or the MD Patients Oriented Severity Index (MD-POSI)).
3. The severity of tinnitus (assessed by means of a standardised method (e.g. VAS, Tinnitus Handicap Inventory)).
4. Perception of aural fullness (assessed by means of a standardised method (e.g. VAS)
5. Quality of life (generic quality of life (e.g. SF-36) and/or disease specific quality of life (e.g. Functional Level Scale, Dizziness Handicap Index)).
6. The incidence of adverse events or complications.

Search strategy

In association with the UK Cochrane Centre, particularly the Ear, Nose and Throat Review Group, we will conduct a systematic search for all SRs for pharmacological and non-pharmacological interventions for MD. We will search the Database of Abstracts of Reviews of Effect (DARE), MEDLINE and EMBASE for SRs, and eligible RCTs will be extracted that examine the efficacy of pharmacological and non-pharmacological therapies in MD. In case several SRs investigate exactly the same treatment modality in the same population, we will extract the RCTs from the most recent published review. As no current worldwide-recommended guidelines exist for the treatment of MD, we intend to include all systematically reviewed interventions. We will use Medical Subject Headings (MeSH) and key words in the search strategy for additional SRs and RCTs. We will use the following keys words with synonymous word: *'Menière's disease'*, *'systematic review', 'randomised controlled trial', placebo controlled trial'*. Details of the search strategy are shown in **Table 1a** and **Table 1b.**

TABLE 1a. Search strategy for systematic reviews for Menière's disease.

#1	exp Meniere disease* [therapy]
#2	systematic review
#3	#1 AND #2
#4	meta-analysis
#6	#1 AND (#3 OR #4)
#7	#3 OR #6

TABLE 1b. Search strategy for randomised controlled trials for Menière's disease.

#1	exp Meniere disease* [therapy]
#2	randomised controlled trial
#3	#1 AND #2
#4	placebo controlled trial
#6	#1 AND (#3 OR #4)
#7	#3 OR #6

Two independent reviewers (BE and HZ) will screen title and abstract for potentially eligible SRs. These will be downloaded for full-text screening and further evaluation. Authors and journal names will be blinded. No restriction on language will be used. After identifying all interventions that were systematically reviewed, we will screen title and abstract for potentially eligible RCTs that were published since the publications of these SRs. Similar to the selection of SRs, these RCTs will be screened on full-text and evaluated. We will remove all duplicate RCTs after full-text screening and reference checking. The reviewers will examine and extract all data from the included RCTs into a data set.

Data extraction

After we selected eligible RCTs, the two reviewers (BE and HZ) will independently extract information from the RCTs on predesigned data-extraction forms. To begin with, we will extract the general information from each RCT covering the country, number of centres, number of participants, study design, the number of treatment arms, allocation ratio, and conflict of interest and funding. Then, study characteristics of the MD patients will be extracted including sex, age, age at onset of disease, subclassification of MD types (diagnostic criteria defined by the AAO-HNS of 1995) and duration and frequency of vertigo attacks before start of treatment. Furthermore, details of the interventions will be extracted for both the experimental and control groups. For the pharmacological interventions we will record the drug category (e.g. anticholamines, diuretics), generic name of the drug, dose per day, way of administration (e.g. oral, intratympanic), additional treatments and period of treatment. In addition, for the non-pharmacological interventions we will extract the type of intervention (e.g. Meniett device, endolymphatic sac surgery) and any additional treatments (pre-study or during trial participation). Last, we will extract information of the effect on the primary and secondary outcome measures and we will record the incidence of adverse events and complications. Study characteristics will be displayed for the intervention arm as shown **Table 2** for pharmacological, for non-pharmacological interventions as shown in **Table 3**. **Table 4** and **Table 5** show the items that will be extracted from the control groups, respectively the placebo and the sham group.

TABLE 2. Study characteristics pharmacological interventions.

Study	Intervention	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	Classification MD	Frequency attacks (per year)	Duration attacks (hrs)	Drug category	Generic name	Dose/ day (mg)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Author et al. year															

TABLE 3. Study characteristics non-pharmacological interventions .

Study	Intervention	Sample size	Sex ratio (♂:♀)	Age (mean ±SD)	Age at onset (mean ±SD)	Classification MD	Frequency attacks (per year)	Duration attacks (hrs)	Additional treatment	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Author et al. year												

TABLE 4. Study characteristics of placebo group in pharmacological intervention studies.

Study	Intervention	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	Classification MD	Frequency attacks (per year)	Duration attacks (hrs)	Drug category	Dose/ day (mg)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Author et al. year														

TABLE 5. Study characteristics of sham group in non-pharmacological intervention studies.

Study	Sham intervention	Sample size	Sex ratio (♂:♀)	Age (mean ±SD)	Age at onset (mean ±SD)	Classification MD	Frequency attacks (per year)	Duration attacks (hrs)	Additional treatment	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Author et al. year												

Outcome assessment

We aim to investigate the efficacy of treatment for MD in controlling vertigo attacks (primary outcome). As defined in the AAO-HNS guideline of 1995 [13], the control of vertigo will be calculated and classified (Class A, 100% control of vertigo, Class B, 40% control of vertigo). Ideally, the primary outcome is again evaluated after 18 and 24 months following randomisation. However, it is unlikely that a placebo-controlled trial will last this long. Therefore, we will include papers that have assessed the efficacy of the therapy reflected by the primary outcome at 3 to 6 months of follow-up. We will ensure accurate assessment of the outcome measures as independent reviewers (BE and HZ) extract the information from the selected RCTs and a third reviewer (TB and/or PB) will check the completeness and correctness of the extracted data.

Risk of bias assessment

We will assess the methodological quality of the RCTs by use of the Cochrane Collaboration's risk of bias tool[14] within Review Manager v. 5.3 software (Review Manager (Revman) v.5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The tool is based on the following eight potential sources of bias: random sequence generation; allocation concealment; blinding of the participants; blinding of the outcome assessors; incomplete outcome data; missing data and selective outcome reporting, other bias (e.g. improper statistical analysis). Two independent reviewers (BE and HZ) will independently evaluate the quality of the RCTs. Each aspect will be graded with 'yes', 'no', or 'unclear', which will reflect a high risk of bias, low risk of bias and unclear risk of bias, respectively. For each study, all eight domains will be evaluated and displayed in a table (see **Table 6**). If there is any disagreement on inclusion or exclusion, this will be settled by discussion, if necessary in the presence of a third reviewer (TB and/or PB). In addition, we will grade the diagnostic validity of studies on the basis of the robustness of the methods used to diagnose the disorder (homogeneity of the types of participants). This grading will form the basis to assess the risk of bias and perform sensitivity analyses. We will grade papers that used the AAO-HNS 1995 criteria for 'definite' and 'certain' MD as 'I'. We will grade studies in which less clear but rigorous criteria were used as 'II'. Studies in which no or less clear diagnostic criteria were used will be graded as 'III'.

TABLE 6. Risk of bias assessment based on the Cochrane risk of bias tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Missing data	Selective reporting	Other bias
... et al. year	High risk or low risk or unclear	idem	Idem	Idem		Idem	idem	

Data analysis

Data will be entered into Review Manager (Version 5.3). For each treatment modality we aim to perform a statistical analysis for the primary outcome comparing the interventional arm to the control group (placebo or sham). In addition, studies that report the vertigo attack frequency as a continuous outcome, we intend to calculate the effect size using the mean difference (MD) or the standardised mean difference (SMD). The same applies for the loss of hearing. When appropriate data will be categorised or dichotomised for control of vertigo, the severity of vertigo attacks, the severity of tinnitus, perception of aural fullness, quality of life, complications and adverse events.

The included studies will be explored on methodological and statistical heterogeneity. The latter will be quantified by the I^2 statistic. An I^2 value greater than 50% is considered to indicate substantial heterogeneity (Handbook 2011, The Cochrane Collaboration) [15]. If the data are sufficiently homogenous, we will pool outcome data. It is expected that the data will carry a certain amount of heterogeneity and a random-effects model will be used. Forest plots will be shown for each intervention. If the data turn out to be too heterogeneous for pooling based on methodological heterogeneity and statistical heterogeneity, we will perform a descriptive review and summarise the available evidence for this intervention. The strength of the evidence will be evaluated by use of the GRADE method as generated by the Cochrane Collaboration. **Table 7** shows the summery of findings per intervention based on the GRADE method.

TABLE 7. Summary of findings per intervention.

Intervention versus control (placebo or sham) for Menière's disease or syndrome						
Type of participants: **Settings:** **Intervention:**						
Outcomes	**Illustrative comparative risks (95% CI)***		**Relative effect[4] (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk[2]	**Corresponding risk[3]**				
	Control	**Intervention**				
Control of vertigo, Follow-up: mean ... months					○○○○	
We will use the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this to the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain. The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of the these factor: study limitations (risk of bias); inconsistency; indirectness of evidence; imprecision and publication bias. This table will be constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We will include the following outcomes in the 'Summary of findings' table: control of vertigo attacks, hearing, severity of vertigo attacks and tinnitus, perception of aural fullness, quality of life and adverse events.						
*The basis for the assumed risk (e.g. the median proportion of patients with control of vertigo related to the follow-up period). The corresponding risk (and its 95% confidence interval is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).						

Dealing with missing data

We expect missing data in the selected trials for the SR. All corresponding authors will be contacted and asked for the original data. If only a per protocol analysis has been carried out, corresponding authors will be contacted for the original data on the intention to treat analysis.

Subgroup analysis

We will perform subgroup analysis to investigate heterogeneity and inconsistency in the selected trials. Subgroup analysis will be performed with regard to subtype of MD ('certain', 'definite', 'probable', or possible' MD in accordance with the AAO-HNS 1995 criteria [13]), stage of disease (as defined by the AAO-HNS 1995 criteria [13]), and duration of treatment. As the primary outcome is a patient reported outcome, blinding can be of influence. Therefore, we will consider the method of blinding the most important subgroup analysis.

Sensitivity analysis

We will perform a sensitivity analysis to address whether the eight potential sources of bias played a relevant role in the robustness of our study findings. Studies with a high risk of bias will be analysed separately to evaluate if the efficacy of the intervention is not solely based on these trials and if trial results are robust.

Publication bias

Publications bias will be explored by performing funnel plots if sufficient data are available (10 or more studies).

ETHICS AND DISSEMINATION

Formal ethical approval is not required, as primary data will not be collected. The findings will be disseminated in peer-reviewed journals and conference presentations.

CONCLUSION

We expect this umbrella systematic review to provide a systematic summary of evidence and we aim to identify the treatment(s) with the highest efficacy for MD and to identify areas for future valuable research.

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Contributors
BE, HZ, TB and PB contributed to the design and conception of the study protocol. The search strategy was developed and run by the ENT Group. BE and HZ will screen studies on title and abstract and full text. If disagreement over inclusion or exclusion arrives, this will be settled by discussion with all authors (BE, HZ, TB and/or PB). BE and HZ will independently extract data from the articles and a third reviewer (TB and/or PB) will check the completeness and correctness of the extracted data of the outcome assessment. All authors drafted and revised this study protocol and approved it for publication.

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Competing interests
None declared.

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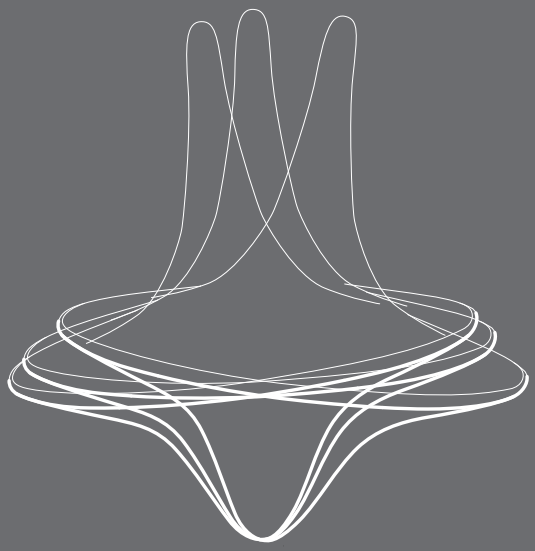

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INTERVENTIONS FOR MENIÈRE'S DISEASE: AN UMBRELLA SYSTEMATIC REVIEW

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Submitted British Medical Journal

ABSTRACT

Objectives: To summarise the efficacy of pharmacological and non-pharmacological treatments for Menière's disease (MD).

Design: Systematic literature review and meta-analysis.

Data sources: An online database search was conducted in association with the UK Cochrane Centre, particularly the Ear, Nose and Throat Group, from inception to June 2016. Reference lists were cross-checked.

Eligibility criteria for selecting studies: Systematic reviews on treatments for MD were screened for eligible interventions. From these systematic reviews, we included randomised controlled trials (RCTs) in patients with MD that compared a pharmacological treatment or non-pharmacological treatment with placebo or sham surgery. A separate search was conducted to identify RCTs on treatment modalities that were systematically reviewed yet published after the conduction of these systematic reviews. The primary outcome was control of vertigo as defined by the American guideline as published in 1995. No language restrictions were applied. The GRADE approach was used to appraise and evaluate the quality of evidence.

Results: We found five systematic reviews from which 19 RCTs were extracted. Five RCTS were added by the separate search resulting in a total of 24 RCTs (n=1091) which evaluated the efficacy of betahistine dihydrochloride, intratympanic injections with gentamicin or steroids, endolymphatic sac surgery and pressure pulse therapy.

Conclusions: Evidence on the efficacy of interventions for patients with MD is generally of low quality. Based on RCTs with a low risk of bias, there is moderate quality of evidence that there is no effect of betahistine and positive pressure therapy. There is inconclusive evidence with regards to efficacy of intratympanic injections with gentamicin or steroids and endolymphatic surgery.

Systematic Review Registration PROSPERO CRD42015024243

INTRODUCTION

Menière's disease (MD) is an inner ear disorder characterised by incapacitating attacks of vertigo accompanied by nausea and vomiting, fluctuating sensorineural hearing loss as well as tinnitus and/or aural fullness. Even though the disease was described as early as 1861 by Prosper Menière [1], there are still many unanswered questions regarding the pathophysiology of the disease. Furthermore, an evidence-based treatment has not been established yet.

The main aim of the treatment in MD is to reduce the frequency and intensity of vertigo attacks and ideally to preserve hearing and vestibular function [2]. Psychological suffering and reduced quality of life are linked to MD, as disabling vertigo attacks can occur without warning [3,4]. Therefore, an effective (prophylactic) treatment is necessary to improve the quality of life of MD patients. Current pharmacological treatment options include betahistine, diuretics, oral steroids and intratympanic application of gentamicin or corticosteroids [5]. However, evidence in terms of reducing vertigo complaints has never been conclusive [6,7,8], except for intratympanic gentamicin treatment [9]. Non-pharmacological treatment options include positive pressure therapy (the Meniett device), ablative surgery such as vestibular nerve section, surgical labyrinthectomy and endolymphatic sac surgery [2,5,10]. Analogous to the pharmacological treatment modalities, high quality evidence is also lacking for non-pharmacological therapies [10,11]. Since so many treatments exist without convincing results, it may be hard for patients and their physicians to select the best available treatment. To date, no systematic review exists that summarises the body of evidence and states implications for clinical practice.

We conducted a systematic review to summarise the efficacy of interventions for MD, to report clinical implications of the results and to identify areas for future valuable research.

METHODS

Protocol and guidance

This protocol is reported in line with PRISMA-P [12] and has been registered at PROSPERO (CRD42015024243) and has been published [13]. Reporting of statistical data followed the Cochrane Collaboration Handbook, version 11. Formal ethical approval is not required as primary data will not be collected.

Eligibility criteria

We included systematic reviews or meta-analyses on the efficacy of pharmacological and non-pharmacological treatments compared with placebo or sham surgery in patients with MD, and extracted the randomised controlled trials (RCTs) for data-analysis. In addition, online databases were checked for eligible RCTs on treatment modalities that

were systematically reviewed yet published subsequent to the date the systematic review was published. We excluded treatment modalities that were not previously evaluated on efficacy by means of a systematic review.

Since the natural course of MD has a waning pattern, time should be regarded as a therapeutic factor when analysing the efficacy of a therapeutic intervention. Therefore, a placebo-controlled design is essential to account for the illusion of therapeutic efficacy. Due to the great variability in the clinical presentation of MD, the disorder is not always easy to diagnose. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines in order to standardise the diagnostic process in MD and to improve comparability of populations when performing trials on patients with MD [13]. In 2015, a new set of diagnostic criteria were jointly formulated by the Classification Committee of the Bárány Society, the Japanese Society of Equilibrium Research, the European Academy of Otology and Neurotology, the AAO-HNS and the Korean Balance Society to facilitate future studies [14]. However, as these international diagnostic criteria were only published recently and previous research widely used the AAO-HNS 1995 diagnostic guidelines, the 1995 set of criteria was used to identify 'definite' Ménière's disease patients in the current review. Ideally, outcomes are evaluated following randomisation with a long follow-up period as the natural course of disease is believed to last up to 20 years. Since we know that only few placebo-controlled trials last this long, we also included papers that assessed the efficacy of the therapy on the short term (up to 3 months) or long term (6 months or more).

Information sources and search strategy

In association with the UK Cochrane Centre, particularly the Ear, Nose and Throat Review Group, we conducted a search for all systematic reviews for pharmacological and non-pharmacological interventions for MD. We searched the Database of Abstracts of Reviews of Effect (DARE), MEDLINE and EMBASE for systematic reviews from which eligible RCTs were extracted. In case several systematic reviews investigated the same treatment modality in the same population, we extracted the RCTs from the most recently published systematic review. We included all systematically reviewed interventions. We also crosschecked the references of potentially eligible RCTs. We used Medical Subject Headings and key words in the search strategy for systematic reviews and additional RCTs. We used the following keywords with the synonymous words: *'Menière's disease'*, *'systematic review', 'randomised controlled trial', 'placebo controlled trial'*. Details of the search strategy are shown in **Table 1a** and **Table 1b.** The last electronic search was conducted in June 2016.

Study selection

Two reviewers (BE and HZ) independently screened title and abstract of the retrieved systematic reviews. No restriction on language was used and disagreements were resolved by consensus or with help of a third reviewer (TB or PB). After identifying all interventions that were systematically reviewed, we screened title and abstract for potentially eligible RCTs that were published since the publications of the selected systematic reviews. Similar to the selection of systematic reviews, these RCTs were screened for eligibility on full-text.

Data collection process

The same two reviewers (BE and HZ), independently extracted data from the RCTs on pre-designed data-extraction forms. Disagreements were resolved by consensus or with the help of a third reviewer (TB or PB). We extracted information on the country, number of enrolling centres, number of participants, study design, number of treatment arms, allocation ratio, and conflict of interest and funding. Then, study characteristics of the MD patients were extracted including sex, age, age at onset of disease, subclassification of MD types (diagnostic criteria defined by the AAO-HNS of 1995) and duration and frequency of vertigo attacks before start of treatment. Details of the interventions were extracted for both the experimental and control groups.

For the pharmacological interventions we recorded the drug category (e.g. anticholamines, diuretics), generic name of the drug, dose per day, way of administration (e.g. oral, intratympanic), additional treatments and period of treatment. For the non-pharmacological interventions we extracted the type of intervention (e.g. Meniett device, endolymphatic sac surgery) and any additional treatments (pre-study or during trial participation). We ensured that an accurate assessment of the outcome measures occurred by having two independent reviewers (BE and HZ) extracting the information from the selected RCTs and having a third reviewer (TB and/or PB) checking the completeness and correctness of the extracted data. When more information was needed, we consulted the published protocols, supplementary material, and press releases of these studies.

Outcome assessment

The primary efficacy outcome was the extent of control of vertigo. As defined in the AAO-HNS guideline of 1995 [13], the control of vertigo was calculated and classified. The number of vertigo attacks in the interval after treatment (Y) was divided by the number of vertigo spells six months prior to treatment (X) and multiplied by 100. The resulting number indicates the extent of 'control of vertigo'. The AAO-HNS further divides the control of vertigo into classes, where Class A (CoV=0) represents a complete control of vertigo and class B (CoV up to 40%) represents a substantial control of vertigo. Assessment

of control of vertigo by any other outcome measure (e.g. mean frequency of vertigo attacks at baseline and at the final assessment) was also accepted.
The secondary efficacy outcomes were hearing (based on the pure-tone audiometry), the severity of vertigo attacks (assessed by means of a standardised method (e.g. the Visual Analogue Scale (VAS) or the MD Patients Oriented Severity Index (MD-POSI)), the severity of tinnitus (assessed by means of a standardised method (e.g. VAS, Tinnitus Handicap Inventory)), the perception of aural fullness (assessed by means of a standardised method (e.g. VAS), the quality of life (generic quality of life (e.g. SF-36) and/or disease specific quality of life (e.g. Functional Level Scale, Dizziness Handicap Index)) and the occurrence of adverse events or complications.

Risk of bias of individual studies

We assessed the methodological quality of the RCTs by use of the Cochrane Collaboration's risk of bias tool[14] within Review Manager v.5.3 software (Review Manager (RevMan) v.5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). We used the following eight potential sources of bias: random sequence generation; allocation concealment; blinding of the participants; blinding of the outcome assessors; incomplete outcome data; selective outcome reporting and other bias (e.g. improper or flawed statistical analysis). Two reviewers (BE and HZ) independently evaluated the quality of the RCTs. Each aspect was rated with a high risk of bias, a low risk of bias or an unclear risk of bias. In case of any disagreement on inclusion or exclusion this was settled by discussion, if necessary in the presence of a third reviewer (TB and/or PB).
We evaluated the homogeneity of the participant included in the studies based on the inclusion criteria used to diagnose MD. Papers that used the AAO-HNS 1995 diagnostic criteria for 'definite' and 'certain' MD as were rated as 'class I'. We rated studies with less clear but still somewhat rigorous criteria as 'class II', for instance 'probable' or 'possible' MD based on the AAO-HNS 1995 criteria. Studies in which no or less clear diagnostic criteria were used were rated as 'class III'. The evaluation formed the basis to perform sensitivity analyses. Due to the high risk of inclusion of patients with diseases other than MD in Class III MD patients, assessments for clinical heterogeneity and pooling of data were restricted to 'Class I' and 'Class II' diagnostic MD categories.
In MD it is unlikely that symptom activity returns to its baseline level after the first treatment period. Therefore, we only used data from cross-over trials if the data prior to the cross-over could be obtained.

Data synthesis

Data were entered into Review Manager. For each treatment modality we aimed to perform a statistical analysis for the primary outcome comparing the interventional arm to the

control group (placebo or sham intervention). From studies that reported the vertigo attack frequency and the effect on hearing as a continuous outcome, we used the mean difference (MD) or the standardised mean difference (SMD). When appropriate, data was categorised or dichotomised for control of vertigo, the severity of vertigo attacks, the severity of tinnitus, perception of aural fullness, quality of life, complications and adverse events. For dichotomous data we calculated the risk ratio (RR).

The included studies were explored on clinical and statistical heterogeneity. The latter was quantified by the I^2 statistic. An I^2 value greater than 50% was considered to indicate substantial heterogeneity (Handbook 2011, The Cochrane Collaboration)[15]. If the data was sufficiently homogenous, we pooled outcome data. No forest plots were calculated for outcomes for which only one study could be retrieved. It was expected that the data would carry a certain amount of heterogeneity and we intended to use a random-effects model. In case data turn out to be too heterogeneous for pooling based on classical, methodological and statistical heterogeneity, we performed a descriptive review and summarised the available evidence for this intervention.

We expected missing data in the selected trials for the systematic review. When indicated, corresponding authors were contacted and asked for the original data in order to estimate missing mean differences or standard deviations. If only a per protocol analysis was carried out, corresponding authors were contacted for the original data and we performed an intention to treat analysis on those data.

We performed subgroup analysis to investigate heterogeneity between the studies. Subgroup analysis was performed with regard to subtype of MD ('certain', 'definite', 'probable', or possible' MD in accordance with the AAO-HNS 1995 criteria [13]), stage of disease (as defined by the AAO-HNS 1995 criteria [13]), duration of treatment and blinding. As our primary outcome is a patient reported outcome, blinding can be of influence. Therefore, we considered the method of blinding the most important potential factor for subgroup analysis.

We performed a sensitivity analysis to address whether the eight potential sources of bias played a relevant role in the robustness of our study findings. Studies with a high risk of bias were analysed separately to evaluate if the efficacy of the intervention was not solely based on these trials and if trial results were robust.

The quality of the evidence was evaluated by use of the GRADE method [16], as recommended by the Cochrane Collaboration. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correctly applied. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that we are very uncertain about any estimate of effect obtained. Several factors

can lead to the downgrading of the quality of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of the following factors: study limitations (risk of bias), inconsistency, indirectness, imprecision and publication bias.

Publication bias

Publications bias was explored by performing funnel plots if sufficient studies were available (10 or more studies).

RESULTS

Study selection

Electronic searches yielded 1560 systematic reviews after removal of duplicates **(Figure 1)**. Titles and abstract were screened and 108 unique reports were selected for full text screening. A total of seven systematic reviews were selected for study assessment; 19 RCTs could be extracted from these reviews. One review involved evaluation of the effect of acupuncture for MD and included three RCTs, but none of the studies were placebo-controlled so they were excluded. One Cochrane review [7] evaluated the effect of diuretics for MD, but did not include any RCTs; therefore this intervention could not be evaluated. As a result, five interventions formed the basis of the current review: three pharmacological and two non-pharmacological interventions. The pharmacological interventions involved oral betahistine dihydrochloride and intratympanic (IT) injections with gentamicin or steroids. The non-pharmacological interventions covered endolymphatic sac surgery and transtympanic positive pressure therapy.

The search we subsequently performed identified three relevant trials. This led to a total of 24 RCTs to summarise the evidence on the efficacy of treatment for patients with MD. Cross-reference checking did not reveal any additional relevant articles.

Study characteristics

Of the 24 trials, 14 were monocentre trials [17-26,31-33,39]. In six studies [17,18,23-26] a cross-over design was used and in the remaining studies a parallel design was used. The number of MD patients varied from 10 to 221 per study as shown in **Tables 2-6**. Overall, the studies involved 1091 participants (n=671 for the pharmacological interventions, and n=420 for the non-pharmacological interventions)

Twelve studies [26,28,31-40] included adults meeting diagnostic class I criteria, five studies [22,25,27,29,30] class II and the remaining class III. The age at inclusion was similar between studies and varied between 36 and 64. The sex distribution was not reported in six studies [18,19,23,28,29,35] and approximately 1:1 in other studies. In none of the selected

studies the age at onset of symptoms was reported. In six studies [20,21,25,27,30,39] the duration of disease was reported which varied between 2.3
and 43 months. The frequency of vertigo attacks was evaluated in four studies [32,33,38,40] and two studies described the duration of attacks [25,30].
In all but four studies [25,26,28,37] the primary outcome involved evaluation of vertigo symptoms. The follow-up duration varied between studies from two weeks to a maximum of 24 months. In none of the selected studies all of our predefined outcomes were evaluated. A total of eight studies evaluated all but one of our predefined secondary outcomes [21,22,28-31,35,36]. Our predefined secondary outcome hearing loss was evaluated in 20 studies [19-29, 31-39], the severity of vertigo attacks in five studies [23,24,31,29,40], tinnitus in six studies [18,19,22,23,29,30] and the perception of aural fullness was assessed in seven studies [21-23,29-31,33]. Disease specific quality of life was assessed in nine studies [26,27,30,33,35-37,39,40]. Adverse events or complications were reported in 14 studies [17,19,21,25-27,30,32-34,36,38-40] varying from 0% to 46% of the study population.

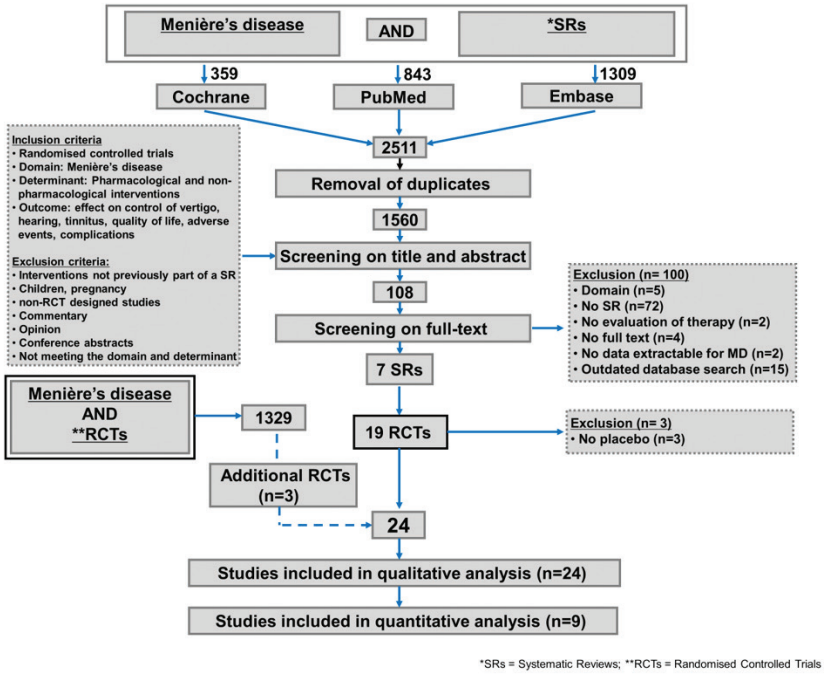


Figure 1. Study flow selection

Risk of bias within studies

The results of the risk of bias assessment are summarised and shown in **Figure 2** (**Appendix** for detailed risk of bias assessment). The three most recently published studies [36,37,40] had a low risk of bias. The blinding of participants, personnel and the outcome and selective reporting was rated as low risk of bias in 20 out of the 22 RCTs. In all but five studies [31,32, 36,37,40] the potential bias associated with random sequence generation and allocation of concealment remained unclear due to a lack of information.

Incomplete outcome data and other sources of bias were considered as high risk in thirteen [17-21,23,24,30,31,33,34,39,40] and fourteen [17,18,20,21,26,27,29-32,34,37-39] studies, respectively. Generally, we considered the item 'other bias' to be of high risk if there were missing baseline values, group differences at the start of the trials, inappropriate or unclear statistical analyses or a combinations of these.

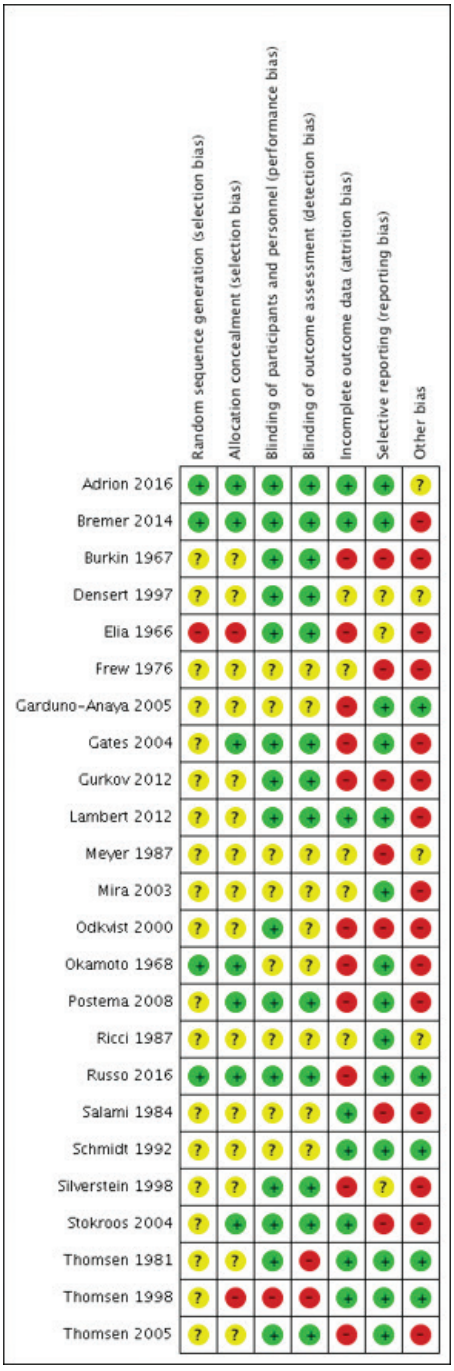
The Cochrane review which analysed the efficacy of endolymphatic sac surgery for MD included results from Bretlau *et al.*[41] and Thomsen *et al.* [25] evaluated the efficacy of this intervention after nine years of follow-up. However, based on the initial publication in 1981 by Thomsen *et al.* [22], there was a high risk of bias since patients were deblinded for treatment arm after a follow-up period of 12 months. Therefore, we included the original trial results from the initial publication, which described the 12-month follow-up.

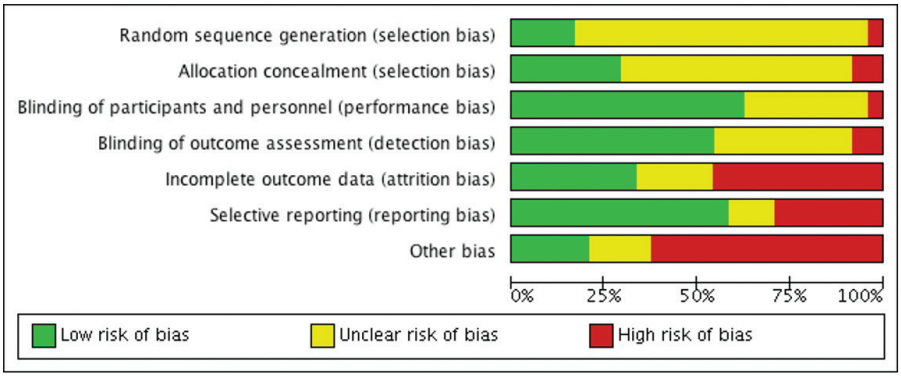
With respect to bias resulting from potential financial conflicts of interest, we found 5 studies [26,30,36,38,39] in which the author(s) had received a mixture of funding from governmental bodies and unrestricted grants from the industry. The study by Gates *et al.* [32] had received support from the Medtronic Xerox industry (manufacturer of the Meniett® device) and the first author had served as a paid consultant to Medtronic Xomed at a scientific retreat in 2000, leading to a potential financial conflict of interest. One of the trials in which patients were treated with IT injections with gentamicin was prematurely discontinued due to serious adverse events in the interventional arm [35].

Synthesis of results

Results of our predefined primary and secondary outcomes are summarised in **Table 7**. Because of clinical heterogeneity in the reporting of the secondary outcome measures, we dichotomised these into a difference reported ('yes'), or no difference reported ('no') instead of noting the absolute differences between intervention and control arm. Results per intervention, including results after assessment of clinical heterogeneity, are summarised in the following sections. To assess the clinical heterogeneity we looked at dissimilarity between studies with regards to patients, intervention, comparison and outcome (PICO).

Figure 2. Risk of bias assessment





Betahistine dihydrochloride

Results on this treatment modality were based on 10 trails [17-21,23,24,26,28,36] and are presented in the **Summary of finding Table 8**. Three trials (n= 353) were graded with class I or class II certainty of the diagnosis [25,30,36], the remaining had a class III certainty of the diagnosis.

One small study reported on the control of vertigo in which a significant proportion of patients reached control of vertigo in the betahistine group compared to the placebo group [18]. It remained unclear which statistical methods were used and no data were presented besides a statistical significant in favour for betahistine was found. We rated the quality of the evidence for this outcome as very low.

Vertigo attack frequency was included as an outcome in three studies in which the follow-up took three, four and nine months [25,30,36]. All studies used a different method to quantify the effect on the monthly vertigo attack frequency. Adrion *et al.* used the individual 30-day standardised attack rate which was based on the number of documented diary days considering that the undocumented days were missing at random [36]. Patients had to have a frequency of two vertigo attacks per month in at least three consecutive months before enrolment. Mira *et al.* described no details on the minimum number of vertigo attacks at the start of the trial [30]. No details on the methods to assess the vertigo attack frequency were reported. Schmidt *et al.* defined the outcome regarding vertigo attack frequency as 'imbalance' [25]. Periods of imbalance were categorised into mild attacks (maximum of 1 minute), moderate attacks (maximum of five minutes) and severe attacks (lasting hours) from which the monthly imbalance frequency was calculated. Due to the great variability on how the outcomes were evaluated data could not be pooled. We rated the quality of the evidence for this outcome as moderate and was summarised narrative.

The effect of betahistine on hearing loss was assessed in seven studies in variable ways. Hearing loss was evaluated based on means with corresponding four-point thresholds for the frequencies from 0.25 kHz to 2.0 kHz by Schmidt *et al.* [25]. Data from the four

remaining studies could not be pooled because only data per frequency were reported and no mean four-point threshold score could be calculated [36], no pre-cross over data were available [23,24], or no data were presented [21]. The remaining two studies evaluated only which patients subjectively improved on their hearing by means of questionnaires [19,20]. Only Schmidt *et al.* reported results in mean four-point threshold scores that found no effect on hearing in favour of betahistine [25]. We graded the quality of the evidence for this outcome as low.

Data on the severity of vertigo attacks was available in two studies [30,36]. In the remaining three studies no pre-cross over data was available in two studies [23,24] and no data were presented by one study [21]. Mira *et al.* used an Italian questionnaire, the GISFaV, which involved evaluation of the intensity, duration and associated symptoms during vertigo attacks [30]. Scores improved significantly after therapy with betahistine (57%) in comparison with placebo (3.1%) ($p<0.0001$). Adrion *et al.* used an ordinal 4-point scale to assess the severity of vertigo which was reported as the estimated coefficients. No significant difference was found between high dose betahistine, low dose or placebo. We rated the quality of the evidence for this outcome as low [36].

All but one study reported changes in tinnitus symptoms before and after treatment [17]. The effect on tinnitus was reported as the loudness in dB by Schmidt *et al.* [25]. Adrion *et al.* used the Mini-Tinnitus Impairment questionnaire [36]. Elia *et al.* used a 4-point visual analogue scale rating tinnitus from 0 as no tinnitus to 4 as severe tinnitus [18]. It remained unclear how post-treatment scores were analysed and no concrete percentage scores of data were presented. The methods to assess the effect on tinnitus were not reported by Mira *et al.* [30]. Subjective changes were reported by Frew *et al.* who used a four-point scale, Meyer *et al.* who used a five-point scale and Okamato *et al.* who used a three-point scale [19,23,24]. Both Ricci *et al.* and Salami *et al.* a scale ranging from 0 to 6 were used [20,21]. Pre-cross over data could not be extracted and no data were presented in four studies [18,20,21,23,24]. Due to the large differences in the remaining four studies on how to measure the effect on tinnitus data were not pooled. Only Mira *et al.* reported a significant effect on tinnitus after treatment [30]. We rated the quality of the evidence for this outcome as low [30].

Mira *et al.* and Schmidt *et al.* presented data on aural fullness as a secondary outcome [25,30]. No pre-cross over data could be extracted in two studies [23,24] whereas no numerical data were presented in two other studies [20,21]. Mira *et al.* reported no details on how the assessment of aural fullness took place without means and standard deviations, but patients who received betahistine improved significantly more on this outcome than patients on placebo [30]. By means of a visual analogue sale, Schmidt *et al.* could not detect a significant difference between the two intervention arms [25]. Due to the lack of information on the comparability of outcomes measurement, data could not be pooled. We rated the quality of the evidence for this outcome as low.

Two studies assessed the dizziness-related quality of life by means of the Dizziness Handicap Inventory (DHI) [30,36]. Results were reported in the absolute mean change differences and in the mean decrease in percentage [36]. Mira *et al.* reported a significant improvement in DHI score after betahistine therapy compared to placebo without mean and standard deviation data. We rated the quality of the evidence for this outcome as low [30].

Intratympanic gentamicin injections

All three RCTs (n= 62) evaluating the effect of IT injection with gentamicin used a class I diagnostic assessment [31,32,37]. Both Postema *et al.* and Stokroos *et al.* reported on the control of vertigo [31,32]. Both studies reported a significantly higher control in vertigo for the gentamicin treated patients (56% and 100%) when compared to placebo (0% in both studies). None of the patients in the placebo group reached control of vertigo. Due to clinical heterogeneity in the number of injections (this was not standardised by Stokroos *et al.*), the interval between the injections and the difference between the study groups at baseline, we did not pool the data [32]. We rated the quality of the evidence for this outcome as low (see **Summary of findings Table 9**).

Stokroos *et al.* reported the yearly vertigo attack frequency before and after treatment [32] in which patients after gentamicin injections reached control of vertigo while the placebo group did not (yearly vertigo attack rate of 11±10). We rated the quality of the evidence for this outcome as very low.

Due to a severe significant hearing loss in one patient, the study of Bremer *et al.* was prematurely ended as was prescribed in the stopping rules [37]. Stokroos *et al.* found no deterioration of hearing due to application of gentamicin and the hearing loss did not progress during trial participation [32]. Postema *et al.* found an increase of hearing loss of 8.1±18.1 dB in the gentamicin group (including a patient with a hearing loss of 60 dB); for the placebo group hearing scores remained stable (0.0 ±0.7 dB). We rated the quality of the evidence for this outcome as very low [31].

The effect on the severity of vertigo attacks, tinnitus and aural fullness was only assessed by Postema *et al.* They found that only the aural fullness improved significantly in the gentamicin group compared with placebo [31]. We rated the quality of the evidence for this outcome as low.

Effect on quality of life was assessed by Bremer *et al.* by means of the DHI, which was comparable in both treatment groups [37]. We rated the quality of the evidence for this outcome as low.

Intratympanic steroid injections

The three RCTs (n=83) evaluating the effect of IT injection with steroids all used class I diagnostic criteria [25,33,38]. Lambert *et al.* compared a high and low dose of OTO-104, a sustained-release formulation of dexamethasone, to placebo [38]. The high dose OTO-104 (12mg) was used as the interventional arm for the analysis. We found clinical heterogeneity between the trials; there was a large difference in the duration of follow-up (varying from 1.5 to 24 months), the number of injections (varying from one to five injections in five consecutive days, to two times three in three consecutive days) and the dose. This heterogeneity precluded us from pooling data.

Garduño-Anaya *et al.* assessed the effect of the intervention on control of vertigo in line with the AAO-HNS guidelines and revealed that 82% of the patients treated with steroids had control of vertigo compared to 57% in the placebo group [33]. We rated the quality of the evidence for this outcome as low (**see Summary of findings table 10**).

Garduño-Anaya *et al.* found a significant decrease in the monthly vertigo attack rate in favour of steroids, whereas the decrease was similar between the OTO-104 and the placebo group in the study performed by Lambert *et al.* [33,38]. We rated the quality of the evidence for this outcome as low.

The mean PTA averages were used to assess the effect on hearing but it remained unclear which frequencies were used to assess the effect on hearing in two studies [33,38]. Authors were contacted by email to verify information on the used frequencies as well as data on standard deviations and standard errors. Lambert *et al.* informed us that the group data was considered as proprietary but due to regulatory restrictions data could not be shared at this time [38]. From the remaining authors no information could be retrieved regarding this matter. No effect on hearing was found by any of the studies. We rated the quality of the evidence for this outcome as low.

The effect on the severity of vertigo attacks was not included by the selected studies.

The effect on tinnitus was measured by the Tinnitus Handicap Inventory (THI) by all three studies and authors were contacted as information on standard deviations was missing. Despite our attempts to verify data, these could not be retrieved before this review was published. Neither study observed a significant improvement on tinnitus when comparing steroids to placebo. We rated the quality of the evidence for this outcome as low

Silverstein et al. assessed the effect on aural fullness in a dichotomous way (presence of aural fullness yes/no) [26]. No pre-cross over or raw data were presented. Garduño-Anaya *et al.* found a favourable outcome for steroids with regards to aural fullness based on a visual analogue scale quantifying the percentage of improvement (from 1 to 100%) [33]. Mean scores without standard deviations were given. We rated the quality of the evidence for this outcome as low.

The dizziness specific quality of life was analysed by means of different questionnaires: the DHI and the MDPOSI (MD patients oriented severity index). Garduño-Anaya *et al.* found a favourable outcome for steroids [33] where as Lambert *et al.* [38] did not find a significant difference in quality of life. Data could not be pooled as only a p-value or mean without standard deviation were given. We rated the quality of the evidence for this outcome as low.

Surgery – endolymphatic sac surgery

The two RCTs (n=59) that evaluated the effect of endolymphatic sac surgery were graded with a class II certainty of the diagnosis [24,27]. Both assessed the effect on control of vertigo after a duration of 12 months, which is in line with the AAO-HNS guideline. Based on the similarity in assessment of the outcome, the duration of follow-up and the certainty of the diagnosis, we pooled data for the control of vertigo outcome which is shown in **Figure 3.** The pooled risk ratio (RR) was 0.94 (95% confidence interval (CI) 0.37 to 2.4; Chi^2 p=0.96, I^2 = 0%) demonstrating no significant favour of endolymphatic sac surgery over sham surgery or tympanic tubes. We rated the quality of the evidence for this outcome as low (**see Summary of findings table 11).**

The vertigo attack frequency and the severity of vertigo attacks were not analysed in the selected studies.

Hearing involved analysis of the frequencies 250-1000 Hz by Thomsen *et al.* 1981 whereas Thomsen *et al.* 1998 included the frequencies 500-4000 Hz [22,27]. Thomsen *et al.*1981 presented no mean or standard deviation data and the author was contacted to verify this information in this matter but data could not be retrieved [22]. In both studies no effect on hearing was found. We rated the quality of the evidence for this outcome as low (see Summary of findings table 11).

With regard to tinnitus, Thomsen *et al.* 1981 used a 4-point Likert scale to investigate the effect whereas Thomsen *et al.* 1998 did not report any details on how the effect size was quantified [22,27]. Both studies found no significant difference on tinnitus. We rated the quality of the evidence for this outcome as low (see Summary of findings table 11).

Only Thomsen *et al.*1981 analysed the effect on aural fullness but failed to demonstrated a difference between the two treatment groups [22]. We rated the quality of the evidence for this outcome as very low.

In line with the AAO-HNS guideline, the FLS was used to quantify the effect on quality of life but no group differences could not be demonstrated. We rated the quality of the evidence for this outcome as very low (see Summary of findings table 11).

Positive pressure pulse therapy

A total of six RCTs (n=424) evaluated the efficacy of positive pressure therapy; the studies were classified as a class I or a class II certainty of diagnosis. Follow-up duration varied from

immediately after applying pressure pulses to 4 months after treatment [28,29,34,35,39,40]. None of the studies evaluated the effect of positive pressure pulse therapy by means of the control of vertigo.

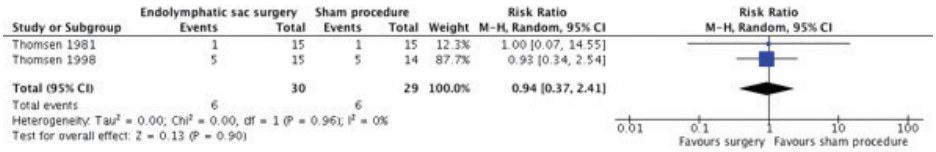


Figure 3. Pooled risk ratio for control of vertigo

Three studies (n=199) investigated the frequency of vertigo attacks. Gates *et al.* [34] used total vertigo scores based on a 5-point visual analogue scale by which a score of 2 or higher indicated a definitive vertigo attack which was assessed at every month for four months. On baseline the mean proportion of days with definitive vertigo attacks was 0.20 (SD 0.17) which decreased to 0.10 (SD 0.14) in the active treatment arm. For placebo the proportion of days with definitive vertigo attacks decreased from 0.24 (SD 0.22) to 0.11 (SD 0.16) resulting in a mean difference of -0.01 (95% CI: -.008 to 0.06, p=0.79). Russo *et al.* evaluated the outcome 48 days after therapy; Thomsen *et al.* evaluated the result after 30 days [35,40]. In both studies participants first received a transtympanic tube and if no control of vertigo was present after 35 days or 2 months, respectively, randomisation took place. This was done in order to eliminate the potential effect of the transtympanic tube on vertigo attacks. In the period after receiving the transtympanic tube and prior to randomisation, patients had to have at least two episodes of vertigo. Based on the similarity in the diagnostic MD classification, duration of follow-up and the method for the assessment of the outcomes, results for these studies were pooled, which is shown in **Figure 4** and is presented in the **Summary of finding table 12**. The pooled mean difference (MD) was -0.67 (95% CI: -2.10 to 0.76, Chi^2 p=0.32, I^2 = 0%) demonstrating no significant favour of the positive pressure therapy over the placebo device. We rated the quality of the evidence for this outcome as moderate.

The remaining studies used either the visual analogue scale without exact data given [28] or a cumulative vertigo score in a period of four months [39]. Due to the differences between measures we were unable to combine the data in a meta-analysis.

Gates *et al.* and Gürkov *et al.* (n=123) evaluated the effect on hearing [34,39]. Both studies used the AAO-HNS criteria for definite MD and analysed mean PTA results over the low frequencies after four months of positive pressure therapy for 5 minutes, three times daily. **Figure 5** shows that the pooled mean difference was 7.38 (95% CI: 2.51-12.25, Chi^2 p=0.09, I^2 = 0%) in favour of the placebo group compared to the active treatment group

for the average low-frequency tones (0.25-1 kHz). We rated the quality of the evidence for this outcome as moderate.

In Ödkvist *et al.* the effect on the severity of vertigo attacks was analysed by means of the visual vertigo analogue scale, which was reported to be significantly improved in the active group compared to the placebo group [29]. No details were shown on data or methods to quantify the effect. We rated the quality of the evidence for this outcome as very low.

Densert *et al.*, Ödkvist *et al.* and Thomsen *et al.* analysed the effect of positive pressure therapy on tinnitus and aural fullness [28,29,35]. All studies analysed the effect by means of a visual analogue scale with any further details. Due to heterogeneity in the duration of treatment, absence of data on means and standard deviations and details on how the outcome was measures, data could not be pooled. In none of these studies an effect was reported on these two outcomes. We rated the quality of the evidence for this outcome as very low.

Both Russo *et al.* and Thomsen *et al.* evaluated the effect on dizziness-related quality of life by means of the Functional Level Scale (FLS) [33,38]. Similar to the vertigo attack frequency we pooled results for this outcome. **Figure 6** shows a pooled MD of -0.54 (95% CI: -1.62 to 0.54, 117 participants, 2 studies, Chi^2 =5.0, I^2=80%), so no significant favour of positive pressure therapy over placebo device use. We rated the quality of the evidence for this outcome as moderate.

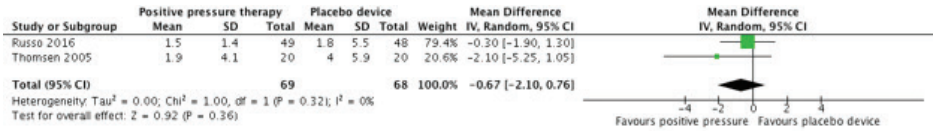


Figure 4. Pooled mean difference on vertigo attack frequency

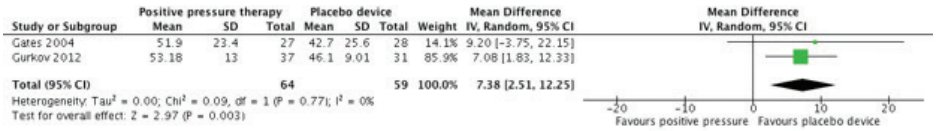


Figure 5. Pooled mean difference on mean pure tone average (PTA)

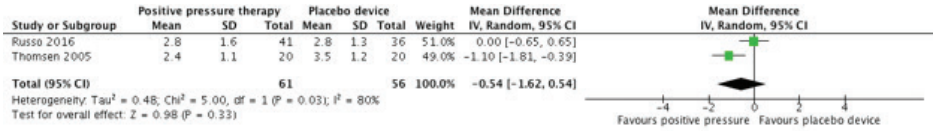


Figure 6. Pooled mean difference dizziness-related quality of life based on the functional level scale (FLS)

Adverse events

Six out of ten trails trials evaluated the efficacy of betahistine compared to placebo and reported data on adverse events (AEs). Occurrence rates could be extracted from three studies, the remaining authors were contacted for information on this matter but no information had yet been provided to us at the time of publication of this review. In 30 out of the 133 participants (23%) in the betahistine group, adverse events were reported compared to 19 out of 131 (15%) in the placebo group [25,30,36]. Duration of treatment varied from 2 weeks to 9 months. Pooling the results gave a risk ratio of 1.35 (95% CI 0.69 to 2.62; 3 studies) as shown in **Figure 7**.

For the studies assessing the adverse effects of IT gentamicin, occurrence rates could be extracted from Bremer *et al.* and Postema *et al.* Hearing loss was found in 29% of the cases (6/21) in the gentamicin group, in which two patients experienced a major complications based on an increase of hearing loss of 50 dB or more [31,37]. In the placebo group an increase of 50 dB in hearing loss was found in one patient (6%, 1/17).

In the IT steroids studies, the occurrence of AEs was reported by Lambert *et al.* Twelve out of 16 high dose OTO-injected patients reported AEs compared to 8 out of 14 in the pooled placebo group [38].

With respect to the non-pharmacological studies, Thomsen *et al.* 1998 reported worsening of MD symptoms in 13% (2/15) of the participants in the endolymphatic sac therapy group compared to 7% (1/14) in the tympanic tube group [27]. Thomsen *et al.* 1981 reported no details on this matter [22].

Data on treatment failure based in the positive pressure pulse therapy group were reported by Gates *et al.* For the positive pressure pulse participants, 3% (1/30) reported themselves as failure compared to 13% (4/32) patients in the placebo group [34].

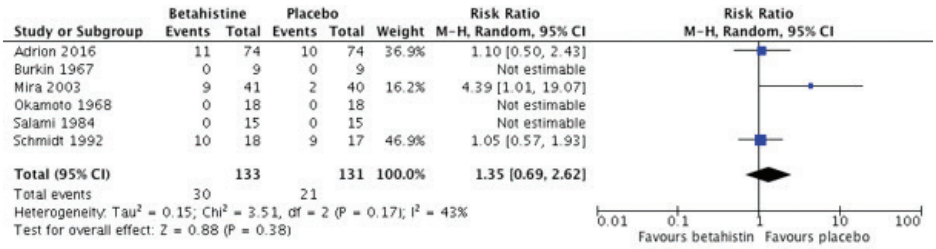


Figure 7. Adverse events

Additional analysis

The number of included studies per intervention and per outcome limited the evaluation of publication bias by means of funnel plots. Data for outcomes in the endolymphatic sac

surgery studies and the positive pressure therapy studies were pooled. However, subgroup analyses were not performed as the grade of certainty of the diagnosis was similar in the selected studies and the stage or the duration of disease was unknown. In the remaining studies, clinical heterogeneity prohibited pooling of data. Sensitivity analyses were not performed due to the fact that only two studies could be pooled per outcome. After removal of the trial with the highest risk of bias, robustness of data would then be based on the results of only one trial.

DISCUSSION

Summary of main results

The objective of this systematic review was to evaluate the efficacy of pharmacological and non-pharmacological interventions for patients with MD. The evidence was generally of low to very low quality. In the following sections the main results per intervention will be summarised and related to results of the GRADE assessment.

Betahistine

Ten studies analysed the effect of betahistine on 402 participants. The studies took place over a period of 2 weeks up to 9 months.

The control of vertigo was analysed in only one study which found a favourable effect of betahistine. However, no data were presented as well as statistical analyses on how a favourable effect was found. The evidence was graded very low mainly due to a high risk of bias with respect to blinding and randomisation, which are known to potentially affect a patient-reported, subjective outcome. The mean vertigo attack frequency showed a small effect but probably not important to patients in favour of betahistine but data should again be interpreted with caution. The evidence is of low quality due to inclusion of patients with diagnoses other than MD and unclear methods on how the effect on vertigo was assessed. Betahistine was generally well tolerated and main adverse events involved gastro-intestinal discomfort, headache and skin rash. Although the pooled risk of adverse events was higher in the betahistine group, quality of the evidence was low and results should be interpreted with caution. With respect to the study results of the high quality study performed by Adrion *et al.* [36] evidence which suggest that betahistine is no more effective than betahistine. A relatively large sample of patients was included in a standardised way and the researchers clearly aimed to assess the effect on vertigo in the most objective way as possible. Due to the inclusion of a placebo arm, a low dose betahistine and high dose betahistine arm, presence of a dose-response relation was investigated. This high quality RCT suggests there is no effect of oral betahistine use for MD in terms of a reduction of vertigo symptoms compared to placebo.

Intratympanic gentamicin injections

Two studies assessed the effect of gentamicin on the control vertigo, but data could not be pooled due to clinical heterogeneity with respect to the number of injections, the interval between the injections, the dose of gentamicin and the interval between the injections. As a result, the evidence for the 'proportion of patients with control of vertigo' was very low. The mean vertigo attack frequency per month was analysed which demonstrated a favour of gentamicin in comparison to placebo, but again due to the low quality of the evidence we have low confidence in the estimated effect. Two studies reported on occurrence rates of adverse events, in which hearing loss was significantly more profound and frequent in the gentamicin group.

Intratympanic steroid injections

The efficacy of intratympanic steroid injections was analysed in three RCTs including 83 participants. One of the studies took place over a maximum of two years so long-term effects of steroids were analysed. The control of vertigo was analysed in one study which found a favourable effect of steroids but as only 18 participants were evaluated based on less favourable statistical analyses, evidence was graded of low quality. Two studies assessed the effect of steroids on the vertigo attack frequency but clinical and methodological heterogeneity data precluded us from pooling. Therefore, the effect of steroids for this outcome remains inconclusive. Patients who had received OTO-104, reported AEs more often than patients in the placebo group. As OTO-104 is still under the approval for treatment purposes, the applicability of the evidence for MD populations worldwide may be considered as limited.

Endolymphatic sac surgery

Results of endolymphatic sac surgery for patients with MD were evaluated in two RCTs which aimed to quantify the efficacy by analysing 59 subjects. Follow-up met the AAO-HNS 1995 guidelines, participants were evaluated up to 12 months after treatment. The pooled risk ratio demonstrated no significant favour of endolymphatic sac surgery over sham surgery or tympanic tubes. Since there was a high risk of bias for allocation concealment, blinding of the participants and researchers, the quality of the evidence was considered to be low. Vertigo symptoms were reported as 'worsened' in 13% in the endolymphatic sac therapy group compared to 7% in the tympanic tube group. Quality of evidence was low based on the fact a single study evaluated this outcome with a small sample size. Moreover, there was a high risk of bias on allocation concealment and blinding of both the participant and the researcher.

Positive pressure therapy

The six RCTs which evaluated the efficacy of positive pressure therapy in MD had 424 participants. None of the selected RCTs evaluated the results on the long term; the maximum follow-up was four months.

The mean vertigo attack frequency was similarly evaluated by two RCTs which resulted in a pooled mean difference of -0.67 (95 CI:-2.10 to 0.76) for positive pressure therapy. However, analysis on statistical heterogeneity revealed high results and therefore, the results should be interpreted with caution.

One RCT reported on the subjective treatment failure which was 3% in the intervention group compared to 13% in the placebo positive pressure group. Due to the fact the study was funded by Medtronic Xerox and non-monitored use of concurrent medical therapy was approved and there was a lack of an intention to treat analyses, the quality of the evidence was graded as low.

Strength and weaknesses of the study

In cooperation with the ENT Group of the UK Cochrane Centre, we used an extensive search strategy to capture all relevant systematic reviews and RCTs. As mainly Cochrane reviews formed the basis for the extraction of all relevant RCTs, it is unlikely that any relevant study has been missed. Moreover, most recent systematic reviews were screened for additional relevant trials.

One may argue whether relevant RCTs have been missed in case these were not part of systematic reviews. Since a relatively small number of placebo-controlled trials were found, it is unlikely that these were not part of previously published systematic reviews.

We used no restriction on language and included both Italian and Japanese papers. Methods are in line with the PRISMA-statement and the protocol was published previously [43]. The roles of all authors were pre-defined in the review process and study selection, extraction of data and assessment on risk of bias was performed independently. Clinical and statistical heterogeneity was analysed before carrying out meta-analysis and we are unaware of any other potential biases in the review process.

Overall completeness and applicability of evidence

The RCTs analysed in this review were generally insufficient to quantify the efficacy of treatment in terms of control of vertigo or mean vertigo attack frequency. Pooled primary outcome analyses included a maximum of three RCTs. Moreover, studies suffered from either clinical or statistical heterogeneity and a high risk of bias. The patients with MD were all conducted in outpatient clinics whereas these patients are also treated in the primary care setting. This limits the applicability of the evidence to patients in these latter settings. We searched all relevant databases and we are confident that all relevant systematic reviews

and RCTs have been included in the current review. We contacted all authors aiming to perceive raw data for pooling of outcomes, unfortunately only information on data was provided by one author at the time of publication of this review.

Quality of the evidence

Overall, the quality of the evidence for the outcomes studied in this review, for the selected five interventions, was low. This means that the estimate of the true effect of future research is likely to be substantially different from the effect measured in the RCTs included in this review. Low quality of the evidence was the result of potential risk of bias, inconsistency, indirectness and imprecision of the effect estimates. Lack of a standardised method of patient recruitment or lack of details on diagnostic criteria, significantly limits the homogeneity between the study populations. With respect to indirectness on the level of the population: in only four out the 24 RCTs a standardised follow-up duration of 12 months or more was used as advised by the AAO-HNS. This restricts applicability of study findings for patients with MD since the disease duration is known to last between 15 to 20 years[42].

The method on evaluation of the outcomes was unclear or differed significantly in the selected studies that precluded us from pooling. Often non-validated questionnaires were used to evaluate subjective changes which can lead to misleading findings.

Last, most studies suffered from imprecision reflected by the wide confidence as results from the small sample sizes and low event rates.

Implications for practice

Evidence on the efficacy of interventions for patients with MD is generally of low to very quality. When results are based on RCTs with the lowest risk of bias, there seems to be no evidence for efficacy of betahistine and positive pressure therapy.

The efficacy of intratympanic injections with gentamicin and steroids remains inconclusive. Results from the RCT with the lowest risk of bias analysed the efficacy of gentamicin but did not include control of vertigo or mean vertigo attack frequency as an outcome. The study ended prematurely due to a significant hearing loss in the gentamicin group that was detected during the interim analysis.

Recently, Patel *et al.* published results of a double-blind RCT comparing intratympanic injections of gentamicin to methylprednisolone with posttreatment follow-up period of 24 months [44]. No clinically relevant and significant difference was found between gentamicin and methylprednisolone in terms of controlling vertigo attacks. Nonetheless, the overall reduction on the vertigo attack frequency was reported to be higher after use of intratympanic injections in comparison to remission in the natural course of disease. So, this study supports the use of intratympanic injections. However, it must be emphasised

that in order to evaluate the efficacy of an intervention in MD, it is imperative to use a placebo-controlled design because of the self-limiting nature of this particular disorder [45]. In line with the authors' conclusion in the Cochrane review [11], we conclude that intratympanic injections with gentamicin may be an effective treatment for vertigo complaints, but it carries a risk of increasing hearing loss because of the ototoxic properties of gentamicin. This is in contrast to steroids, in which no substantial risk of hearing loss seems to be apparent.

We suggests clinical guideline developers should recommend that the choice between steroids or gentamicin should be based on the concept of 'shared decision making' since the scientific evidence for efficacy is inconclusive. For instance, the amount of hearing loss could serve as in indication for either treatment. Since a risk of hearing loss after treatment with gentamicin exists, patients with still a serviceable hearing may be treated with steroids. The report by Browning states that the threshold of more than 30dB hearing level defines a 'socially acceptable' hearing. In case of profound hearing loss gentamicin injections can be considered [46].

With respect to endolymphatic sac surgery, low quality RCTs provided insufficient evidence for a beneficial effect on vertigo. Recently, the effect of endolymphatic duct blockage (EDB) compared to endolymphatic sac decompression has been evaluated in a prospective cohort study by Saliba *et al.* Although promising results for EDB were found, further research needs to quantify the effect of this intervention [47]. No placebo-controlled trials were found which evaluated the efficacy of diuretics, vestibular nerve section or surgical labyrinthectomy.

Implications for future research

Due to the low quality of evidence of RCTs on intratympanic injections the efficacy, the optimal dose and the frequency of injections remains to be further elucidated preferably by means of a placebo-controlled trial with a gentamicin and a steroids interventional arm. Moreover, efficacy could also be evaluated by means a trial including a lower and a higher dose to verify if a dose-response relationship exist which suggests that a therapeutic effect is present. With respect to endolymphatic sac surgery (either decompression or duct blockage), ethical restrictions are likely to complicate the execution of double-blind designed studies that include sham surgery. Randomised controlled trials in which surgery is compared to a less invasive treatment and analysed by a blinded outcome assessor is blinded may still provide useful information.

We propose that a randomised controlled trial evaluating the efficacy of gentamicin and steroids should be a priority in the research field of MD, and it should preferably include a placebo-arm. Based on the fact that high quality evidence reveals ineffectiveness of betahistine, there is an urgent call for an alternative. Since the indication for endolymphatic

sac surgery is restricted to smaller group of patients, i.e. patients unresponsive to conservative treatment and intratympanic injections, this will limit applicability of study findings and lowers feasibility of the study.

It is imperative that the added value of therapy remains disputable due to lack of knowledge on the natural course of the disease. However, the incapacitating character of the disease makes it unethical to refrain from treatment [48]. As a result, there is limited information regarding the natural course of the disease, which jeopardises treatment effects in the absence of a placebo. Due to the new set of diagnostic criteria formulated in 2015, future research regarding patients with MD has the ability to significantly increase homogeneity between study populations. An online prospective registration system of patients' characteristics may provide relevant information on epidemiological aspects of the disease as well as worldwide use of therapy. We recommend the development of outcomes considered most relevant to patients (patient-reported outcomes) in this field. Involving patients, healthcare professionals, researchers, and representatives from the industry to prioritise research, facilitates future collaborations for the recruitment of adequate sample sizes to significantly increase the quality of evidence in the field of MD.

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Contributors

BE, HZ, TB and PB contributed to the design and conception of the study protocol. The search strategy was developed and run by the ENT Group. BE and HZ screened studies on title and abstract and full text. If disagreement over about eligibility arrived occurred, this was settled by discussion with all authors (BE, HZ, TB and/or PB). BE and HZ independently extracted data from the articles and a third reviewer (TB and/or PB) checked the completeness and correctness of the extracted data of the outcome assessment. All authors drafted and revised this study protocol and approved it for publication.

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TABLE 1a. Search strategy for systematic reviews for Menière's disease.

#1	exp Meniere disease* [therapy]
#2	systematic review
#3	#1 AND #2
#4	meta-analysis
#6	#1 AND (#3 OR #4)
#7	#3 OR #6

TABLE 1b. Search strategy for randomised controlled trials for Menière's disease.

#1	exp Meniere disease* [therapy]
#2	randomised controlled trial
#3	#1 AND #2
#4	placebo controlled trial
#6	#1 AND (#3 OR #4)
#7	#3 OR #6

TABLE 2. Details of included studies

Author	Trial period	Country	Study design	No of centres	No of patients	No of treatment arms	Primary outcome	Allocation ratio	Conflict of interest	Funding
Adrion *et al.* 2016[34]	March 2008 -November 2012	Germany	RCT, double-blind, parallel	14	221	Three; high dose, low dose and placebo	Number of vertigo attacks per 30 days	1:1:1	None known	German Federal Ministry of Education and Research; German Centre for Vertigo and Balance Disorders, University Hospital of Munich
Burkin *et al.* 1967[17]	NR	USA	RCT, double-blind, cross-over	Monocentric	22	Two; betahistine versus placebo	Reduction in duration of vertigo	1:1	None known	NR
Elia *et al.* 1966[18]	NR	USA	RCT, double-blind, cross-over	Monocentric	20	Two; betahistine versus placebo	Vertigo reduced with betahistine	1:1	None known	NR
Frew *et al.* 1976[23]	NR	The Netherlands	RCT, cross-over	Monocentric	22	Two; betahistine versus placebo	Severity of vertigo	1:1	None known	NR
Mira *et al.* 2003[28]	Jan 1999-June 2001	Italy	RCT, double-blind, parallel	11	144, 81 with Menière's disease	Two; betahistine versus placebo	Number of vertigo attacks/ month	1:0.9	None known	Grant from Grunenthal-Formenti, Milan, Italy
Meyer *et al.* 1985[24]	NR	Berlin	RCT, cross-over	Monocentric	44	Two, betahistine versus placebo	Subjective change in vertigo	1:1	None know	NR

TABLE 2. Continued.

Author	Trial period	Country	Study design	No of centres	No of patients	No of treatment arms	Primary outcome	Allocation ratio	Conflict of interest	Funding
Okamoto *et al.* 1968[19]	1967, April-September	Japan	RCT, double-blind, parallel	1	36	Two; betahistine versus placebo	Reduction in frequency of vertigo attacks	1:1	None known	NR
Ricci *et al.* 1987[20]	NR	Italy	RCT, double-blind, parallel	Monocentric	10	Two; betahistine versus placebo	Control of vertigo class	1:1	None known	NR
Salami *et al.* 1984[21]	NR	Italy	RCT, double-blind, parallel	Monocentric	30	Two; betahistine versus placebo	Number of vertigo attacks	1:1	None known	NR
Schmidt *et al.* 1992[26]	NR	The Netherlands	RCT, double-blind, cross-over	Monocentric	35	Two; betahistine versus placebo	Imbalance based on objective evaluation	1:1	None known	NR
Bremer *et al.* 2014[37]	June 2009-January 2012	The Netherlands	RCT, double-blind, parallel	2	15	Two; intratympanic gentamicin versus placebo	Dizziness Handicap Inventory	1:1	None known	No source of funding
Postema *et al.* 2008[30]	NR	The Netherlands	RCT, double-blind, parallel	Monocentric	28	Two; intratympanic gentamicin versus placebo	Vertigo complaints on a 4-point Likert-scale	1:1	None known	NR
Stokroos *et al.* 2004[30]	October 2000-October 2002	The Netherlands	RCT, double-blind, parallel	Monocentric	22	Two; intratympanic gentamicin versus placebo	Control of vertigo symptoms	1:1	None known	NR

TABLE 2. Continued.

Author	Trial period	Country	Study design	No of centres	No of patients	No of treatment arms	Primary outcome	Allocation ratio	Conflict of interest	Funding
Garduño-Anaya *et al.* 2005[33]	Nov 2000-July 2003	Mexico	RCT, double-blind, parallel	Monocentric	24	Two; intratympanic steroids versus placebo	Change in frequency of vertigo, control of vertigo class	1:1	None known	NR
Lambert *et al.* 2012[38]	1 year	USA	RCT, double-blind	15	44	Three; intratympanic OTO-104 high dose versus low dose versus placebo	Mean change in vertigo attack frequency	1:1:1	None known	Otonomy, Inc Statistical Analyses, financial compensation
Silverstein *et al.*1998[26]	NR	USA	RCT, double-blind, cross-over	Monocentric	17	Two; intratympanic steroids versus placebo	Hearing loss	1:1	None known	Grant from Ear Research Foundation
Thomsen *et al.* 1981[22]	9 years	Denmark	RCT, double-blind, parallel	Monocentric	23	Two; endolymphatic sac surgery versus Regular mastoidectomy, no removal of bone over endolymphathic sac	Control of vertigo class	1:1	None known	NR
Thomsen *et al.* 1998[27]	NR	Denmark	RCT, double-blind, parallel	2	29	Two; endolymphatic sac shunt versus ventilation tube	Frequency and duration of vertigo attacks	1:1	None known	NR

TABLE 2. Continued.

Author	Trial period	Country	Study design	No of centres	No of patients	No of treatment arms	Primary outcome	Allocation ratio	Conflict of interest	Funding
Densert *et al.*1997[28]	NA (immediate FU)	Sweden	RCT, double-blind	2	39	Two; portable air pressure generator versus sham air pressure generator	Electrocochlear responses	1:1	None known	NR
Gates *et al.* 2004[34]	February 2002-April 2003	USA	RCT, double-blind, parallel	4	62	Two; Meniett device versus sham Meniett device	Vertigo symptoms	1:1	Medtronic Xomid (pressure generator producer) granted the trial	Medtronic Xomid
Gürkov *et al.* 2012[39]	Nov 2004-Nov 2008	Germany	RCT, double-blind, parallel	Monocentric	74	Two; Meniett® device versus sham Meniett® device	Vertigo diary scores (number of vertigo days, vertigo-free days, sick days)	1:1	None known	NR
Ödkvist *et al.* 2000[29]	NR	Sweden	RCT, double-blind	4	56	Two; Meniett® device versus sham Meniett® device	Frequency and intensity of vertigo attacks	1:1	None known	NR
Rosso *et al.* 2016[40]	NR	France	RCT, double-blind, parallel	17	97	Two; Meniett® device versus sham Meniett® device	Frequency and intensity of vertigo attacks	1:1	None known	Medtronic Xomid delivered Meniett devices
Thomsen *et al.* 2005[35]	NR	Sweden, Denmark, Norway	RCT, double-blind, parallel	8	40	Two; Meniett® device versus sham Meniett® device	Frequency of vertigo attacks	1:1	None known	NR

TABLE 3. Study characteristics of patients in pharmacological interventions studies – interventional arm.

Study	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks	Drug category	Generic name	Dose/ day (mg)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Adrion *et al.* 2016[36]	73	1:0.9	56.1±11.1	NR	Class I	NR; At least two attacks/ month in the three months prior to the trial, no details shown	NR	Antihistamine	Betahistine dihydrochloride (Vasomotal, Abbott Pharma, Hannover, Germany)	48mg (2x24mg: 1xBH+PB;2xPL; BH+PB)	Oral	225.8±89.0 days, Intended FU 9 months	Drug discontinuation due to AE 15%	0%
	74	1:1.1	56.1±12.6	Idem	Class I	NR; Idem	NR	Antihistamine	Idem	144mg (3x48mg)		215.8±98.8 days, Intended FU 9 months	Drug discontinuation due to AE 6%	0%
Burkin *et al.* 1967[17]	11	1:1	47.1±5.1	NR	Class III	NR	1 wk to 10 wks	Antihistamine	Betahistine dihydrochloride	16 mg (4x4mg)	Oral	2 weeks	No	No
Elia *et al.* 1966[18]	10	NR	NR	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	16 mg (4x4mg)	Oral	2	NR	NR
Frew *et al.* 1976[23]	11	NR	NR	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	19 mg (2x8 mg)	Oral	9	NR	NR
Mira *et al.* 2003[30]	41	NR; betahistine group 1:1.3	NR; betahistine group 46.9±13.1	Duration of disease 31.6±55.0 months	Class II	NR	NR	Antihistamine	Betahistine dihydrochloride	16 mg (2x8mg)	Oral	3	28% betahistine group, 21% Menière's disease patients	No
Meyer 1985 *et al.*[24]	20	1:1.05	NR, 24-67	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	36 mg (3x 6 mg)	Oral	3	NR	NR
Okamoto *et al.* 1968[19]	18	NR	NR	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	6mg (3x12mg)	Oral	2 weeks	No	No

TABLE 3. Continued.

Study	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks	Drug category	Generic name	Dose/ day (mg)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Ricci *et al.* 1987[20]	5	1:1.5	36.4±2.2	Duration of disease 39.2±7.3 months	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride (Microser)	24 mg (3x8mg)	Oral	10.4±1.2	NR	NR
Salami *et al.* 1984[21]	15	1:1.1	49.6±4.0	Duration of disease 2.3±0.4 months	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride (Microser, Prodotti Formenti)	24 mg (3x8mg)	Oral	2 months, FU 6 months	No	NR
Schmidt *et al.* 1992[25]	18	1:0.8	49.5±10.1	Duration of disease 8.9±8.4	Class II	NR; at least one vertigo attacks in the month prior to the trial	NR	Antihistamine	Sustained-release betahistine dihydrochloride	24 mg (3x8mg)	Oral	8	46% (total study duration; before and after cross-over)	One patient stopped due to side-effects
Bremer *et al.* 2014[37]	5	1:0.7	64.5±8	Duration of disease 3.1(0.1-19.6) yrs	Class I	NR	>20 min	Aminoglycoside	gentamicin	40mg/mL (x3)	Four weekly intratympanic injections	Intended FU 24 months	20% (n=1/5)	Hearing loss >30dB injected side
	4	1:0	72.6±5	Duration of disease 3.3(0.7-7.5) yrs	Class I	NR	>20 min	Aminoglycoside; saline solution	Gentamicin; natrium chloride 0.9%	40mg/mL (x2)	Four weekly intratympanic injections	Intended FU 24 months	0% (0/4)	No
Postema *et al.* 2008[31]	16	NR	Median 55	NR	Class I	NR	>20 min	Aminoglycoside	gentamicin	30mg/mL (x1)	Four weekly Intratympanic injections via middle ear tube	12	NR	NR
Stokroos *et al.* 2004[32]	12	NR	59(34-74)	NR	Class I	74±114	>20 min	Aminoglycoside	gentamicin	30mg/mL (x1)	Intratympanic injections	6-28	0%, recurrence of vertigo n=1)	No

TABLE 3. Continued.

Study	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks	Drug category	Generic name	Dose/ day (mg)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Complications
Gardun-Anaya *et al.*2005[33]	11	1:2.7	49.0±16.8	NR	Class I	0.87±0.61 attacks/ month	>20 min	Corticosteroid	Steroids	4mg/mL (4x)	Intratympanic injections, 1, 6, 12, 18 and 24 months	24	0%	No
Lambert *et al.* 2012[38]	14	NR	53.0(26-60)	NR	Class I	7.3±5.98 (28 days to injections)	>20 min	Corticosteroid	Steroids, OTO-104	3 mg/mL (1x)	Intratympanic injections	3	0%	No
	16	NR	55.5(22-70)	NR	Class I	8.0±5.43(28 days to injections)	>20 min	Corticosteroid	Steroids, OTO-104	12 mg/mL (1x)	Intratympanic injections	3	0%	No
Silverstein *et al.*1998[26]	10	NR	NR	NR	Class I	NR	>20 min	Corticosteroid	Steroids	0.2-0.3mL, 8 mg/ mL (1x)	Intratympanic injections	1.5	33% (n=5) reported worsening of their MD symptoms	No

TABLE 4. Study characteristics of patients in pharmacological intervention studies – placebo arm.

Study	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks	Drug category	Generic name	Dose/ day (mg/ mL)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Compli-cations
Adrion *et al.* 2016[36]	74	1:1.1	54.5±12.8	NR	Class I	6.2±6.9 attacks per 30 days	NR	NA	NR, identical in appearance to betahistine	NA, 3x/ day, 2 tablets	Oral	222.5±87.5 days; intended FU 9 months	Drug discontinuation due to AE 7%	0%
Burkin *et al.* 1967[17]	11	1:1	45.5±7.3	NR	Class III	NR	1 wk to 10 wks	NA	NR, identical appearance to betahistine	NA, 4x/ day	Oral	1	No	No
Elia *et al.* 1966[18]	9	NR	NR	NR	Class III	NR	NR	NA	NR, identical appearance to betahistine	NA, 4x/ day	Oral	2	NR	NR
Frew *et al.* 1976[23]	11	NR	NR	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	19 mg (2x8 mg)	Oral	9	NR	NR
Mira *et al.* 2003[30]	40	NR; betahistine group 1:1.6	NR; betahistine group 48.8±14.3	Duration of disease 32.5±67.3 months	Class II	NR	NR	NA	NR, identical appearance to betahistine	NA, 2x/ day	Oral	3	22% placebo group; 5% Menière's disease patients	No
Meyer *et al.* 1985[24]	20	1:1.05	NR, 24-67	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	36 mg (3x 6 mg)	Oral	3	NR	NR
Okamoto *et al.* 1968[19]	18	NR	NR	NR	Class III	NR	NR	Antihistamine	Betahistine dihydrochloride	6mg (3x12mg)	Oral	0.5	No	No
Ricci *et al.* 1987[20]	5	1:0.3	37.0±5.4	Duration of disease 32.8±10.0	Class III	NR	NR	NA	No details reported	NA, 3x/ day	Oral	7.0±1.3	NR	No
Salami *et al.* 1984[21]	15	1:2	42.7±3.5	Duration of disease 6.2±2.0 months	Class III	NR	NR	NA	No details reported	NA, 3x/ day	Oral	2	No	NR

TABLE 4. Continued.

Study	Sample size	Sex ratio (♂:♀)	Age (mean±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks	Drug category	Generic name	Dose/ day (mg/ mL)	Way of administration	Period treatment (months, mean ±SD)	Adverse events (%)	Compli-cations
Schmidt *et al.* 1992[23]	17	1:0.2	49.1±7.5	Duration of disease 5.6±6.4	Class II	NR; at least one vertigo attacks in the month prior to the trial	NR	NA	Capsule identical appearance to betahistine	NA, 3x/ day	Oral	8	48% (total study duration; before and after cross-over)	One patient stopped due to side-effects
Bremer *et al.* 2014[35]	5	1:4	57.3±16.7	Duration of disease 2.5(0.1-18.2) yrs	Class I	NR	>20 min	NA	Natrium chloride 0.9% solution	40mg/mL (2x)	Four weekly intratympanic injections	Intended FU 24	0% (0/5)	Hearing loss (>30 dB)
Postema *et al.* 2008[31]	12	NR	Median 53	NR	Class I	NR	>20 min	NA	NR	NR (1x)	Four weekly Intratympanic injections via middle ear tube	12	NR	NR
Stokroos *et al.* 2004[32]	10	NR	58(45-70)	NR	Class I	25±13	>20 min	NA	NR (buffer solution)	NR (1x)	Six weekly intratympanic injections	6-28	0%	No
Gardun-Anaya *et al.* 2005[33]	7	1:2.5	50.1±13.8	NR	Class I	0.76±0.64 attacks/ month	>20 min	NA	NR	NR (4x)	Intratympanic injections, 1, 6, 12, 18 and 24 months	24	0%	No
Lambert *et al.* 2012[38]	14	NR	47.0(22-70)	NR	Class I	8.4±7.35 (28 days to injections)	>20min	NA	NR	NR (1x)	Intratympanic injections	3	0%	No
Silverstein *et al.*1998[26]	7	NR	NR	NR	Class I	NR	>20 min	NA	Saline and sodium hyaluronate	0.2-0.3 of a 1:1 mixture (1x)	Intratympanic injections	1.5	33% (n=5) reported worsening of their MD symptoms	No

TABLE 5. Study characteristics of patients in non-pharmacological intervention studies – interventional arm.

Study	Intervention	Sample size (n)	Sex ratio (♂:♀)	Age (mean ±SD/ range	Age at onset (mean ±SD/range)	MD Class	Frequency attacks	Duration attacks (hrs)	Additional treatment	Period treatment (months, mean ±SD)	Adverse events (%)	Compli-cations
Thomsen *et al.* 1981[22]	Endolymphatic sac surgery	11	1:1.2	59(38-69)	NR	Class II	>1 attack/per 2 weeks (min. 26 attacks/year	NR	No	109 (FU assessment at 9 years)	NR	NR
Thomsen *et al.* 1998[27]	Endolymphatic sac shunt	15	1:0.7	50(39-69)	Duration of symptoms (1-21 years	Class II	NR	NR	No	12 (last FU assessment)	13%	Severe hearing loss
Densert *et al.*1997[28]	Portable air pressure generator	21	NR	NR(20-65)	>1 year but <6 years	Class I	NR	>20 min but <24 hrs[13]	No	Immediately after pressure therapy	NR	NR
Gates *et al.* 2004[34]	Meniett® device	30	1:3	49.7±9.0	NR	Class I	>2/month in the 2 months prior to the trial	NR	1500mg/d sodium diet	FU assessment at 4 months	Declared as failure 3%	No
Gürkov *et al.* 2012[39]	Meniett® device	38	1:1	57(24-85)	Duration disease in months 43(5-186)	Class I	>2/month in the 2 months prior to the trial		Pre-existing therapy with betahistine 48mg-72mg/ day	FU assessment at 4 months	No	No
Ödkvist *et al.* 2000[29]	Meniett® device	31	NR	NR	NR	Class II	NR	NR	NR	FU assessment at 2 weeks	NR	NR
Russo *et al.* 2016[40]	Tympanic tube, Meniett® device	49	1:1.2	50 (SE1.9)	NR	Class I	3.2 SE 0.4	NR (>20 min)	No	FU assessment at 35 days, 56 days and 77 days	NR	NR
Thomsen *et al.*2005[35]	Meniett® device	20	NR	NR	NR	Class I; stage 2 or 3	8 attacks/year; ≥2 attacks in the 2 months prior to the trial	>20 min	NR	FU assessment at 2 months	NR	NR

TABLE 6. Study characteristics of patients in non-pharmacological intervention studies – sham arm.

Study	Intervention	Sample size	Sex ratio (♂:♀)	Age (mean ±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks (hrs)	Additional treatment	Period treatment (months, mean ±SD)	Adverse events (%)	Compli-cations
Thomsen *et al.* 1981[22]	Regular mastoidectomy, no removal of bone over endolymphathic sac	12	1:1	61(38-74)	NR	Class II	>1 attack/ per 2 weeks (min. 26 attacks/year	NR	No	109 (FU assessment at 9 years)	NR	NR
Thomsen *et al.* 1998[27]	Ventilation tube	14	1:3.7	53(27-71)	NR	Class II	NR	NR	No	FU assessment at 12 months	7%	No
Densert *et al.*1997[28]	Placebo air pressure generator	18	NR	NR(20-65)	>1 year but <6 years	Class I	NR	>20 min but <24 hrs[13]	No	Immediately after pressure therapy	NR	NR
Gates *et al.* 2004[34]	Meniett device	32	1:3.2	49.7±9.0	NR	Class I	>2/month in the 2 months prior to the trial	NR	1500mg/d sodium diet	FU assessment at 4 months	Declared as failure 12.5%	No
Gürkov *et al.* 2012[39]	Meniett® device, three times daily	36	1:0.9	57(24-85)	Duration disease in months 57(4-276)	Class I	>2/month in the 2 months prior to the trial	>20 min but <24 hrs[13]	Pre-existing therapy with betahistine 40mg-72mg/day	FU assessment at 4 months	No	No
Ödkvist *et al.* 2000[29]	Meniett® device for two weeks	25	NR	NR	NR	Class II	NR	NR	NR	FU assessment at 2 weeks	NR	NR

TABLE 6. Continued.

Study	Intervention	Sample size	Sex ratio (♂:♀)	Age (mean ±SD)	Age at onset (mean ±SD)	MD Class	Frequency attacks	Duration attacks (hrs)	Additional treatment	Period treatment (months, mean ±SD)	Adverse events (%)	Compli-cations
Russo *et al.* 2016[38]	Tympanic tube, Meniett® device	49	1:1.5	52 (SE1.6)	NR	Class I	4.3 SE 0.6	NR (>20 min)	No	FU assessment at 35 days, 56 days and 77 days	NR	NR
Thomsen *et al.*2005[35]	Meniett® device	20	NR	NR	NR	Class I, stage 2 or 3	8 attacks/ year; ≥2 attacks in the 2 months prior to the trial	>20 min	NR	FU assessment at 2 months	NR	NR

TABLE 7. Results of primary and secondary outcomes

Intervention	Study	MD Class	Sample size	Period treatment (months)	No (%) control of vertigo intervention	Difference in vertigo attack frequency (mean difference)	Effect on hearing yes/no	Effect on severity of vertigo attacks yes/no	Effect on tinnitus yes/no	Effect on aural fullness yes/no	Effect on QoL yes/no
Betahistine	Adrion *et al.* 2016[36]	Class I	221 (73:74:74)	Mean 7.4	NR	Individual 30-day standardised attack rate High B 5.1-3.8 MD=1.3 Low B 5.8-3.7 MD=2.1 P 6.2 –3.1 MD=3.1	No	No	No	NR	No
	Burkin *et al.* 1967[17]	Class III	18(9:9)	1	22%(4/9):0%(0/9)	NR	NR	NR	NR	NR	NR
	Elia *et al.* 1966[18]	Class III	16(7:9)	0.5	65%(4/7):0%(0/9)*	NR	NR	NR	Yes	NR	NR
	Frew *et al.* 1976[23]	Class III	22 (11:11)	9	NR	NR	Yes	Yes	Yes	Yes	NR
	Mira *et al.* 2003[30]	Class II	81(41:40)	3	NR	Monthly vertigo frequency Baseline versus 3 months B 7.1±9.6 – 2.3±3.2 MD=4.8 P 5.9±7.2 – 5.0±5.9 MD=0.9	NR	56.9% vs 3% (p,0.0001) GISFaV†	Yes	Yes	Yes. -45.7% betahistine vs -30% placebo; p=0.00 (DHI)
	Meyer *et al.* 1985[24]	Class III	40 (20:20)	3	NR	NR	Yes	Yes	Yes	Yes	NR

TABLE 7. Continued.

Intervention	Study	MD Class	Sample size	Period treatment (months)	No (%) control of vertigo intervention	Difference in vertigo attack frequency (mean difference)	Effect on hearing yes/no	Effect on severity of vertigo attacks yes/no	Effect on tinnitus yes/no	Effect on aural fullness yes/no	Effect on QoL yes/no
	Okamoto *et al.* 1968[19]	Class III	36(18:18)	0.5	‡Significant difference based on a combined frequency/ severity outcome	NR	No	‡Significant difference based on a combined frequency/ severity outcome	Yes	NR	NR
	Ricci *et al.* 1987[20]	Class III	10 (5:5)	10.4±1.2	60%(3/5):0%(0/5)	NR	No	NR	No	No	NR
	Salami *et al.* 1984[21]	Class III	30 (15:15)	2	NR	§Significant difference on cumulative vertigo frequency B per month/person 27.2-2.4=25 P per month/person 29.2- 26.4=2.8	No	Yes	Yes	Yes	NR
	Schmidt *et al.* 1992[25]	Class II	35(18:17)	8	NR	Baseline versus 4 months ¶B 21.1(9.3-46.3) 6.9(2.3-17.9) MD =14.2 P 17.5(8.7-34.4)-6.2(2.1-15.4) MD = 11.3	No	NR	No	No	NR
IT gentamicin	Bremer *et al.* 2014[37]	Class I	14(5:4:5)	Premature end of trial	NR	NR	Deterioration of hearing loss	NR	NR	NR	No

TABLE 7. Continued.

Intervention	Study	MD Class	Sample size	Period treatment (months)	No (%) control of vertigo intervention	Difference in vertigo attack frequency (mean difference)	Effect on hearing yes/no	Effect on severity of vertigo attacks yes/no	Effect on tinnitus yes/no	Effect on aural fullness yes/no	Effect on QoL yes/no
	Postema *et al.* 2008[31]	Class I	28(16:12)	12	56%(9/16):0%(0/12)	NR	No	No	No	Yes	NR
	Stokroos *et al.* 2004[32]	Class I	22(12:10)	6-28	100%(12/12) :0%(0/10)	Yearly vertigo attack frequency 74±114 - 0=MD 74 25±31 - 11±10=MD 24	No	NR	NR	NR	NR
IT steroids	Garduno-Anaya *et al.* 2005[33]	Class I	18(11:7)	24	82%(9/11):57%(4/7)	#Mean monthly vertigo attack rate (baseline vs 24 months) Dexa MD=0.84 P MD=0.86	No	NR	No	Yes	In favour of steroids (FLS p<.001, DHI p<0.008)
	Lambert *et al.* 2012[38]	Class I	44(16:14:14)	3	NR	P MD=-0.16 Low dose MD=-0.15 How MD=-0.23	No	NR	No	NR	No (MPOSI)
	Silverstein *et al.*1998[26]	Class I	17(10:7)	1.5	NR	NR	No	NR	No	No	NR
Endolympathic sac surgery	Thomsen *et al.* 1981[22]	Class II	30(15:15)	12	7%(1/15):7%(1/15)	NR	No	NR	No	No	NR
	Thomsen *et al.* 1998[27]	Class II	29(15:14)	12	(33%)5/15:36%(5/14)	NR	No	NR	No	NR	FLS score 1 E 33% 5/15 TT 36% 5/14

TABLE 7. Continued.

Intervention	Study	MD Class	Sample size	Period treatment (months)	No (%) control of vertigo intervention	Difference in vertigo attack frequency (mean difference)	Effect on hearing yes/no	Effect on severity of vertigo attacks yes/no	Effect on tinnitus yes/no	Effect on aural fullness yes/no	Effect on QoL yes/no
Positive pressure therapy	Densert *et al.*1997[28]	Class I	39 (21:18)	Immediately after therapy	No significant difference based a combined frequency/ severity outcome^	No significant difference between based a combined frequency/severity outcome^	No	No significant difference based a combined frequency/ severity outcome^	No	No	NR
	Gates *et al.* 2004[34]	Class I	62(30:32)	4	NR	NR; mean frequency of days with vertigo/ month	Mean low average PTA M 56.5±19.7 – 51.9 ±23.4 P 51.5±18.7 – 42.7 ±25.6	NR	NR	NR	NR
	Gürkov *et al.* 2012[39]	Class I	74(38:36)	4	NR	NR; mean frequency of days with vertigo/ month	Mean low average PTA after 4 months M 53.18±13.0 P 46.10±9.0	NR	NR	NR	No (cumulative activity score)
	Ödkvist *et al.* 2000[29]	Class II	56(31:25)	0.5	NR	Visual analogue scale was used without definition of outcome**	NR	**Idem	**Idem	**Idem	NR
	Rosso *et al.* 2016[40]	Class I	97(48:49)	1.5 (48 days)	NR	Mean 21-days vertigo attack frequency M 3.2-1.5 = MD1.7 P 4.3-1.8 = MD 2.5	NR	NR	NR	NR	Mean FLS score M 4.3±0.09 – 2.8 0.25 P 4.5±0.1 – 2.8±0.22

TABLE 7. Continued.

Intervention	Study	MD Class	Sample size	Period treatment (months)	No (%) control of vertigo intervention	Difference in vertigo attack frequency (mean difference)	Effect on hearing yes/no	Effect on severity of vertigo attacks yes/ no	Effect on tinnitus yes/no	Effect on aural fullness yes/no	Effect on QoL yes/no
	Thomsen *et al.* 2005[35]	Class I; stage 2 or 3	40(20:20)	1	NR	Mean vertigo attack frequency M 9.6 SE6.7 -1.9 SE 4.1 = MD 7.7 P 10.5 SE 8.2 - 4.0S E 5.9 = MD 6.5	No	NR P	No	No	Mean FLS score M 4.2 SE 1.1-2.4 SE 1.1 P 4.SE 0.9-3.5SE1.2 = MD 0.6

MD/ SMD = mean difference/standardised mean difference; NR= not reported

* Control of vertigo was considered to be present in case vertigo symptoms scores were 0 (=no symptoms), evaluated after a treatment of 2 weeks; results are based recalculation on raw data

†The GISFaV involves a subjective rating scale evaluating intensity, duration and associated symptoms related to vertigo attacks. Results were not specified per subgroup, only the total score was given.

‡By means of an ordinal scale vertigo attack frequency were analysed without information on absolute control of vertigo rates.

§Cumulative weekly vertigo attack frequency difference per week per group (n=15) were verified from bar graphs; cumulative rates were divided by 15 and multiplied by 4 to calculate the cumulative vertigo attack frequency/per person/per month.

¶ Results resemble the monthly score vertigo attacks, pre cross-over data were used to analyse mean differences.

Raw data-analysis included those patients who abandoned treatment (intention-to-treat analysis). Results indicate a significant difference in baseline vertigo attack frequency.

** The visual analogue scale was used without definition for the outcome vertigo attack frequency, tinnitus and aural fullness.

TABLE 8. GRADE assessment table betahistine compared to placebo for Menière's disease

Patient or population: Menière's disease **Setting**: Outpatient clinics **Intervention**: Betahistine **Comparison**: placebo						
Outcomes	**Illustrative comparative risks*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	**Betahistine**				
Control of Vertigo follow up: up to 8 weeks	Study population		**Not estimable**	16 (1 RCT)	⊕○○○ VERY LOW[1]	The study describes a significant effect on the control of vertigo in favour of betahistine although no numerical data or statistical analyses were given.
Monthly vertigo attack frequency (individual 30-day attack rate, monthly vertigo attack rate, imbalance score per month) follow up: up to 9 months	Study population		**Not estimable**	259 (3 RCTs)	⊕⊕⊕○ MODERATE[2]	Two studies out of three studies found no significant difference between treatment with betahistine and placebo, including one high quality trail.
Effect on hearing assessed with PTA (pure tone average) follow up: up to 8 months	The mean hearing loss score was 47.8 in the control group	The mean hearing loss score was 9.9 dB higher in the intervention group	**MD 10.10** (-0.97, 21.17)	35 (1)	⊕⊕○○ LOW[3]	

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	**Illustrative comparative risks*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	**Betahistine**				
Effect on severity of vertigo assessed with: Questionnaire Scale from: 0 to 100 follow up: up to 9 months	Study population		**Not estimable**	225 (2 RCT)	⊕⊕○○ LOW[3]	Two studies evaluated the outcome, one reporting a significant effect in favour of betahistine; one found no difference between betahistine and placebo based on estimated coefficients. Studies used defined different outcomes to evaluate the effect on severity of vertigo.
Effect on tinnitus assessed with: Visual analogue scale, loudness in dB, mini tinnitus impairment questionnaire follow up: range 0.5 months to 9 months	Study population		**Not estimable**	276 (4 RCTs)	⊕⊕○○ LOW[4]	Three out of four studies found no difference on tinnitus after treatment with betahistine, one study reported a significant effect in favour of betahistine but no detailed numerical data were presented, all used different outcome measures.
Effect on aural fullness assessed with: visual analogue scale either included in a questionnaire or evaluated separately follow-up: range 3 months to 9 months	Study population		**Not estimable**	225 (2 RCTs)	⊕⊕○○ LOW[5]	One study found no difference on aural fullness after treatment with betahistine, one study reported a significant effect in favour of betahistine but no detailed numerical data were presented, both used different outcome measures.

Patient or population: Menière's disease
Setting: Outpatient clinics
Intervention: Betahistine
Comparison: placebo

Outcomes	**Illustrative comparative risks*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	**Betahistine**				
Effect on Quality of Life (QoL) assessed with: DHI Scale from: 0 to 100% follow up: up to 9	Study population		**Not estimable**	225 (2 RCTs)	⊕⊕○○ LOW[5]	One (high quality) study found no difference on the DHI after treatment with betahistine, one study reported a significant effect in favour of betahistine but no detailed numerical data were presented, both used different outcome measures.
Adverse events follow up to 3 months	**Study population 138 per 1000**	**237 per 1000** (111 to 420)	**RR 1.72** (0.78 to 3.75)	117 (2 RCTs)	⊕⊕○○ LOW[3]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level due to an unclear overall risk of bias in the selected study, downgraded one level to indirectness (the diagnostic criteria were classified as class III), downgraded one level due to imprecision and unclear methods on power calculation and lack of baseline characteristics.
2. Downgraded graded one level due to inconsistency on (one study had a benefit for betahistine and the other two found no difference between either treatment)
3. Downgraded one level due to study limitations (unclear risk of bias for sequence generation, allocation concealment and blinding); downgraded one level due to the level of uncertainty of the diagnosis (use of class II diagnostic criteria).
4. Downgraded graded one level due to unclear overall risk of bias in two studies and a high risk of bias in one study, downgraded one level due to indirectness (diagnostic criteria were classified as Class II in two studies and Class III) in one study).
5. Downgraded graded one level due to inconsistency on (one study had a benefit for betahistine and the other for placebo) and downgraded one level due to indirectness (diagnostic criteria were classified as Class II in both studies).

TABLE 9. GRADE assessment table intratympanic gentamicin injections compared to placebo for Menière's disease.

Patient or population: Menière's disease **Setting: Outpatients clinics** **Intervention: Intratympanic Gentamicin Injections** **Comparison: Placebo**						
Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Gentamicin Injections**				
Control of vertigo (CoV) assessed with: Study form follow up: range 6 months to 28 months	Study population		**Not estimable**	50 (2 RCTs)	⊕⊕○○ LOW[1]	Both studies found a favourable effect for gentamicine but different treatment schedules (interval between injections, injection frequency) precluded us from pooling.
Yearly vertigo attack frequency follow up: to 28 months	Study population		**Not estimable**	22 (1 RCT)	⊕○○○ VERY LOW[2]	The number of vertigo attacks per year decreased to zero in the gentamicin group and to 11±10 for the placebo group.

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Intratympanic Gentamicin Injections
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Gentamicin Injections**				
Hearing loss follow up: range 6 to 28 months	Study population		**Not estimable**	62 (3 RCTs)	⊕⊕○○ LOW[1]	One study pre-maturely ended due to significant hearing loss, one study reported no difference between study group and one reported a difference between study groups with a p-value.
Tinnitus assessed with: Visual Analogue Scale follow up: 12 months	The mean tinnitus score was **2.2**	The mean tinnitus score in the intervention group was 0,1 higher (-0.46 to 0.66)	**Mean difference 0.10** (-0.46 to 0.66)	28 (1 RCT)	⊕⊕○○ LOW[3]	

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Intratympanic Gentamicin Injections
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Gentamicin Injections**				
Aural Fullness assessed with: Visual Analogue Scale follow up: 12 months	The mean aural Fullness was **1.8**	The mean aural Fullness in the intervention group was 0,9 higher (-1.72 to -.08)	**MD 0.90** (-1.72 to -0.08)	28 (1 RCT)	⊕⊕○○ LOW[3]	
Dizziness Handicap Index assessed with: DHI follow up: prematurely ended	Study population		**Not estimable**	10 (1 RCT)	⊕⊕○○ LOW[4]	One study which pre-maturely ended reported no difference between gentamicin or placebo

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Intratympanic Gentamicin Injections
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Gentamicin Injections**				
Adverse events f follow up range 6 to 28 months	59 per 1.000	**227 per 1.000** (36 to 699)	**RR 4.7** (-0.60 to 37.13)	38 (2 RCTs)	⊕⊕○○ LOW[3]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
RR: risk ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level due (lack of standardization concerning the number of injections, the interval between the injections and the gentamicin dosage in one study) and one level due to imprecision.
2. Downgraded one level due indirectness with respect to the intervention (lack of standardization concerning the number of injections, the interval between the injections and the gentamicin dosage), downgraded on level due to imprecision and RoB (high risk of selective reporting - relapse of complaints was left unmentioned).
3. Downgraded one level due to risk of bias (unclear and incorrect statistical analyses) and downgraded on level due to imprecision.
4. Downgraded one level due to imprecision and downgraded on level due to risk of bias (selective reporting - unclear how many patients were screened and finally selected before trail enrollment).

TABLE 10. GRADE assessment table intratympanic steroids injections compared to placebo for Menière's disease.

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Intratympanic Steroids Injections
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Steroids Injections**				
Control of vertigo (CoV) follow up: 24 months	571 per 1.000	**817 per 1.000**	**RR 1.43** (0.71 to 2.88)	18 (1 RCT)	⊕⊕○○ LOW[1]	
Monthly vertigo attack rate assessed with: Daily diary follow up: range 3 months to 24 months	Study population		**Not estimable**	50 (2 RCTs)	⊕⊕○○ LOW[1]	One study found a significant effect on the monthly vertigo attack rate; one study reported no difference between steroid or placebo.
Hearing assessed with: Pure Tone Average follow up: range 1.5 months to 24 months	Study population		**Not estimable**	67 (3 RCTs)	⊕⊕○○ LOW[1]	In none of the studies an effect on hearing was found. No raw data could be extracted.

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Intratympanic Steroids Injections
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Steroids Injections**				
Tinnitus assessed with: Tinnitus Handicap Inventory score, follow up: range 3 months to 24 months	Study population		**Not estimable**	67 (3 RCTs)	⊕⊕○○ LOW[1]	In none of the studies an effect on tinnitus was found. No raw data could be extracted.
Aural fullness assessed with: Visual Analogue Scale for % of improvement, presence of aural fullness (yes/no) follow up: range 1.5 months to 24 months	Study population		**Not estimable**	18 (1 RCTs)	⊕⊕○○ LOW[1]	Favourable effect for steroids over placebo were found without raw data, or mean with corresponding standard deviations.

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Intratympanic Steroids Injections
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Intratympanic Steroids Injections**				
Quality of life assessed with: the Dizziness Handicap Index, the MPOSI follow up: range 3 months to 24 months	Study population		**Not estimable**	67 (3 RCTs)	⨁⨁◯◯ LOW[1]	One study found a significant favourable effect, one study found no difference between steroids and placebo

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level due to risk of bias with regards to complete case analysis and lack of intention-to-treat analysis (overestimation of true effect) and one level due to imprecision.

TABLE 11. GRADE assessment surgery compared to sham surgery for Menière's disease.

Patient or population: Menière's disease **Setting**: Outpatients clinics **Intervention**: Surgery **Comparison**: Sham Surgery						
Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Sham Surgery	**Risk with Surgery**				
Control of vertigo (Class A) (CoV) assessed with: Daily vertigo frequency follow up: 12 months	207 per 1.000	**194 per 1.000**	**RR 0.94** (0.37 to 2.41)	59 (2 RCTs)	⊕⊕○○ LOW[1]	
Hearing assessed with: Pure Tone Average follow up: 12 months	Study population		**Not estimable**	59 (2 RCTs)	⊕⊕○○ LOW[1]	No effect on hearing was found in both studies.
Tinnitus assessed with: Visual analogue scale follow up: 12 months	Study population		**Not estimable**	59 (2 RCTs)	⊕⊕○○ LOW[1]	No significant effect was found in both studies.
Aural fullness assessed with: Visual Analogue Scale follow up: 12 months	Study population		**Not estimable**	29 (1 RCT)	⊕○○○ VERY LOW[2]	No significant effect was found in favour of surgery. No data was presented.

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Surgery
Comparison: Sham Surgery

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Sham Surgery	**Risk with Surgery**				
Quality of Life assessed with: Functional Level Scale follow up: 12 months	357 per 1.000	**332 per 1.000** (121 to 907)	**RR 0.93** (0.34 to 2.54)	29 (1 RCT)	⨁◯◯◯ VERY LOW[2]	
Adverse events follow up: 12 months	71 per 1.000	**134 per 1.000**	**RR 1.87** (0.19 to 18.38)	29(1 RCT)	⨁◯◯◯ VERY LOW[2]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level due to indirectness (diagnostic criteria were classified as Class II) and one level due to imprecision.
2. Downgraded one level due to indirectness (diagnostic criteria were classified as Class II, one level due to imprecision and downgraded one level due to a high risk of bias on performance bias (no blinding of patients or outcome assessment).

TABLE 12. GRADE assessment table positive pressure therapy compared to placebo for Menière's disease.

Patient or population: Menière's disease **Setting**: Outpatients clinics **Intervention**: Positive Pressure Pulse Therapy **Comparison**: Placebo						
Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Positive Pressure Pulse Therapy**				
Mean vertigo attack frequency assessed with: Patient diary follow up: range 1 to 1.5 months	The mean vertigo attack frequency was 2.2	The mean tinnitus in the intervention group was 0.49 higher (-1.56 to 0.59)	**Mean differrence -0.49** (-1.56 to 0.59)	137 (2 RCTs)	⊕⊕⊕○ MODERATE[1]	
Effect on hearing (Hearing) assessed with: Pure Tone Average, low frequency follow up: mean 4 months	The mean PTA low frequency was 4.44	The mean PTA low frequency in the intervention group was 7.36 higher (2.64 to 12.1)	**Mean differrence 7.36** higher (2.64 to 12.1)	123 (2 RCTs)	⊕⊕⊕○ MODERATE[1]	
Severity of vertigo attacks assessed with: Visual analogue scale follow up: 2 weeks	Study population		**Not estimable**	56 (1 RCT)	⊕○○○ VERY LOW[2]	A significant improvement on the severity of vertigo attacks was found. No data were shown.

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Positive Pressure Pulse Therapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Positive Pressure Pulse Therapy**				
Tinnitus assessed with: Visual Analogue Scale follow up: immediately after therapy up to 2 months	Study population		**Not estimable**	135 (3 RCTs)	⊕○○○ VERY LOW[2]	No effect in favour of positive pressure pulse therapy was found. No data on means and standard deviations were given.
Aural fullness assessed with: Visual Analogue Scale follow up: immediately after therapy up to 2 months	Study population		**Not estimable**	135 (3 RCTs)	⊕○○○ VERY LOW[2]	No effect in favour of positive pressure pulse therapy was found. No data on means and standard deviations were given.
Functional Level Scale (FLS) assessed with: Standardised questionnaire follow up: range 1 months to 1.5 months	The mean FLS score was 3.2	The mean FLS score was 0.44 lower (-1.35 to 0.48)	**Mean difference 0.44** (-1.35 to 0.48)	137 (2 RCTs)	⊕⊕⊕○ MODERATE[1]	

Patient or population: Menière's disease
Setting: Outpatients clinics
Intervention: Positive Pressure Pulse Therapy
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Positive Pressure Pulse Therapy**				
Adverse events follow up: mean 4 months	145 per 1.000	**39 per 1.000** (10 to 145)	**Relative risk 0.24** (0.06 to 1.00)	123 (2 RCTs)	⨁⨁◯◯ LOW[3]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Downgraded one level due to risk of bias (overestimation of effect by lack of intention to treat analysis).
2. Downgraded graded two levels due risk of bias (one level for high risk of bias and an unclear risk of bias in two studies and downgraded one level due to use of a non-validated outcome measure with unclear statistical analysis on this outcome in two studies).
3. Downgraded two levels due risk of bias (overestimation of effect by lack of intention to treat analysis and one level due to the risk at conflict of interest (funder of study is Medtronic Xerox.

APPENDIX

TABLE 1. Risk of bias assessment based on the Cochrane risk of bias tool – pharmacological studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Adrion *et al.* 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
	Random sequence list generated 1:1:1 ratio, stratified by site	Concealment allocation was performed by an Internet based randomisation schedule stratified by study site, fixed block size was three which was not disclosed during the trial, random list was generated by an investigator with no clinical involvement in the trial	Blinded for allocation	Blinded for allocation	Intention to treat analysis and per protocol analysis, reason for drop outs reported	All predefined outcomes were analysed	Pre-randomisation attack frequency was not documented although considered as an inclusion criterion. Data was not shown with respect to duration and age at the onset of disease but groups were well balanced based on these characteristics.

TABLE 1. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Burkin *et al.* 1967	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
	Method of randomisation not reported	Method of allocation concealment not described	No details on how double-blinding was achieved	No details on how double-blinding was achieved	No information, no information on follow-up was specified	There was no protocol available. The outcome listed in the material and methods section of the article were all reported in the results section of the article.	No details on statistical analyses were given on how group differences after therapy were calculated and whether these results were statistically significant.
Elia *et al.* 1966	Unclear risk	Low risk	High risk	High risk	High risk	Low risk	High risk
	No details on whether the physician was unaware of the sequence generation.	Uninvolved fifth person generating sequence	The same sequence was repeated (A, B, C and D) was used in all patients, could be predicted by the patients, physician and the statistician.	The same sequence was repeated (A, B, C and D) was used in all patients, could be predicted by the patients, physician and the statistician.	4 out of 20 participants dropped out due to non-compliance to the trial and change of location of the participants.	There was no protocol available. The outcome listed in the material and methods section of the article are all reported in the results section of the article.	No baseline values were given, unclear if groups were adequately balanced prior to treatment; unclear which statistical analysis were performed

TABLE 1. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Frew *et al.* 1976	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Physician could break the code if relapse occurred. Unclear if and in how many cases this occurred, blinding cannot be assured.	No details on the method of blinding of the outcome assessors were given.	Unclear why six patients withdrew, described as "unable to co-operate", no reasons for drop-out were described.	Not all predefined outcomes were reported after assessment by the investigator. Unclear why not all outcomes were summarised by the investigator.	One-sided testing which should be two-sided, standard deviation not reported; high risk of selection bias due to pre-treatment period, allowing the investigator to exclude placebo responders (decreases external validity of study results).
Mira *et al.* 2003	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk
	Unclear who made and kept the randomisation list	Method of allocation concealment not described	In the materials and methods section is was mentioned that this was a double-blind trial. However, the authors did not report who was blinded for what.	In the materials and methods section was mentioned that this was a double-blind trial. However, the authors did not report who was blinded for what.	The number of included participants evaluated is not mentioned in the results and therefore it is unclear whether the evaluated number of participants was the same as the number of participants after initial allocation to the treatment groups.	All predefined outcomes were analysed	No references on the determination of the sample size calculation were available; improvement of associated symptoms including tinnitus, fullness of the ear, nausea and vomiting are summarised in one figure whereas it remains unknown how calculations were performed, unknown if complete data was available

TABLE 1. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Meyer *et al.* 1985	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk
	No details on sequence generation	No details on allocation concealment	Unclear which methods were undertaken to maintain blinding of participant and personnel	No details on the method of blinding of the outcome assessors were given.	Impaired walking pattern was reported for only 38 participants out of 40, which implies missing data although no details on this matter were reported (5%).	Not all outcomes were predefined and details on how these were assessed (tinnitus, gate disturbances and aural fullness)	Inclusion of patients was based on several additional diagnostic test although it remains unclear which diagnostic criteria were mandatory to full fill the diagnosis of Meniere's disease, unclear which statistical analysis were used for each outcome
Okamoto *et al.* 1968	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	High risk
	Use of a random number table	Use of a random number table by central allocation	In the discussion it was claimed that both patients and doctors were unaware of the drug they had been given, however the authors did not report who was blinded for what.	In the discussion it was claimed that both patients and doctors were unaware of the drug they had been given, however the authors did not report who was blinded for what.	4 dropouts out of 40 patients (10%), not due to adverse effects of the drug, but no further details described.	There was no protocol available, the outcomes listed in the method section of the article were all reported in the results section	Medication supplied by Eisai Co; unclear what the role of the subsidising party was

TABLE 1. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ricci *et al.* 1987	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk
	Assigned to the treatment groups based on a randomisation list but methods of randomisation were not reported.	Method of allocation concealment not described	Method of blinding not reported	Method of blinding not reported	No drop outs or lost to follow-up was reported	There was no protocol available. The outcome listed in the material and methods section of the article are all reported in the results section of the article	No information was available regarding the performed statistical analyses
Salami *et al.* 1984	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Method of blinding not reported	Method of blinding not reported	No lost to follow-up or drop outs were reported but it remains if all patients were evaluated during the analysis for all outcomes	There is no protocol available. The outcome listed in the material and methods section of the article are all reported in the results section of the article	Frequency of vertigo attacks (200/month) atypical for Menière's disease

TABLE 1. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Schmidt *et al.* 1992	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Method of blinding not reported	Method of blinding not reported	Reasons for drop outs described, including an intention to treat analysis.	There was no protocol available. The outcomes listed in the material and methods section of the article are all reported in the results section of the article.	Intention to treat analysis not applied because one patient crossed over due to side effects earlier than the protocol described but the data were analysed per protocol. Follow-up data from drop outs was not accounted for.
Bremer *et al.* 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk
	Random sequence generation	Computer generated list	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Preterm stop of trial due to serious adverse events, reasons were given	All predefined outcomes were analysed	Unknown how many eligible patients were screened were not randomised (selection bias)
Postema *et al.* 2008	Unclear risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk
	Methods of randomisation not reported	Randomisation sequence know by one person of the trial	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Reason for drop-out unknown	None known	Inappropriate statistical analysis

TABLE 1. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Stokroos *et al.* 2004	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk
	Methods of randomisation not reported	Randomisation sequence know by one person of the trial	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	No drop outs	Vertigo relapse was present in one patient which was not presented in the result section	No standardisation of intervention and follow-up period as injections were repeated until control of symptoms or one of the exclusion criteria were met. Groups differed significantly with respect to mean attacks per year.
Garduno-Anaya *et al.* 2005	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Method of blinding not reported	Complete case analysis, lack of intention-to-treat analysis (overestimation of true effect)	All predefined outcomes were analysed	Inappropriate statistical analysis
Lambert *et al.* 2012	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Detailed procedure on maintenance of blinding	All data were presented in full appropriate manner	All predefined outcomes were analysed	No parallel inclusion of high and low dose of OTO-104 subjects although analyses were performed as such, no detailed instruction on method of injection

TABLE 1. Continued.

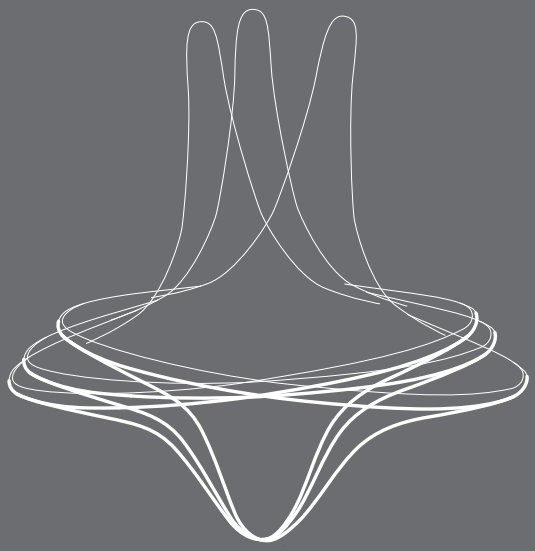
Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Silverstein *et al.*1998	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Three patients dropped out, without reason given.	All predefined outcomes were analysed	No baseline values were given, unclear if groups were adequately balanced prior to treatment

TABLE 2. Risk of bias assessment based on the Cochrane risk of bias tool – non-pharmacological studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Thomsen *et al.* 1981follow-up roken after 12 month ther university peration	Unclear risk	Unclear risk	Low risk	High risk	Low risk	Low risk	Low risk
	Method of randomisation not reported	Method of allocation concealment not described	Patients were unaware of the presence of a placebo operation	The code was broken after 12 month of follow-up	No drop-outs	All predefined outcomes were assessed	This appears to be free of other sources of bias
Thomsen *et al.* 1998	Unclear risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
	Method of randomisation not reported	Sealed envelopes, opened at the start of surgery	Not blinded for the intervention	Not blinded for the intervention	No drop-outs	All predefined outcomes were assessed	This appears to be free of other sources of bias
Densert *et al.* 1997	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Patients dropped out, without reason given.	Insufficient information to permit judgement	No baseline values were given, unclear if groups were adequately balanced prior to treatment
Gates *et al.* 2004	Unclear risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk
	Method of randomisation not reported	Study monitor only received coded information	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Lack of intention to treat analysis, risk of overestimation of true effect	All predefined outcomes were assessed	Risk at conflict of interest (funder of study is Medtronic Xerox), inappropriate statistical analysis, use of concurrent medical therapy without monitoring
Gürkov *et al.* 2012	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	Low risk
	Method of randomisation not described	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Lack of intention to treat analysis, risk of overestimation of true effect	This appears to be free of bias	This appears to be free of other sources of bias

TABLE 2. Continued.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ödkvist *et al.* 2000	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	High risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Method of blinding could not be evaluated	Lack of intention to treat analysis, risk of overestimation of true effect	Inadequate presentation of results (no scale, mean with standard deviation or 95% CI were given	No baseline values were given, unclear if groups were adequately balanced prior to treatment, only *t*-test were performed
Russo *et al.* 2016	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
	Random block randomisation, list with random numbers	Clear method of allocation concealment	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Lack of intention to treat analysis, risk of overestimation of true effect	All predefined outcomes are reported	This appears to be free of other sources of bias
Thomsen *et al.* 2005	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	High risk
	Method of randomisation not reported	Method of allocation concealment not described	Detailed procedures on maintenance of blinding	Detailed procedures on maintenance of blinding	Lack of intention to treat analysis, risk of overestimation of true effect, reasoning for drop-outs not described	All predefined outcomes were assessed	Inadequate presentation of results (no scale, mean with standard deviation or 95% CI were given)



12

GENERAL DISCUSSION

INTRODUCTION

The aims of this thesis were to explore the clinical aspects, to evaluate diagnostic tests and to systematically review the evidence for the effectiveness of interventions for MD. Due to the fact the Apeldoorn Dizziness Centre (ADC) was founded in 2000, a significant number of MD patients have visited the ADC at the time this thesis project was initiated in November 2014. As a result, both retrospective and prospective cohorts could be analysed as approximately 80 to 90 MD patients visit the ADC every year.
In the first paragraph, the main findings per part of the thesis are summarised. Clinical relevance and implications are described in the second paragraph. Third, suggestions for future research are provided. Last, a number of concluding remarks are given.

MAIN FINDINGS OF THIS THESIS

Part I

While previous worldwide research on the age of onset of patients with MD generally found a peak incidence in the fourth and fifth decade of life [1,2] as well as in the seventh decade of life [3], data on the age of onset of MD patients in the Netherlands were lacking (chapter 2). Recently, a 24-year retrospective survey in Japan [3] reported a progressive increase in the age at which MD manifests itself. It was suggested that work-related stress attributes to the development of MD [3,4]. We assessed the age of onset and whether, similar to the Japanese data, a shift in age of onset was also present in the Netherlands. We could not detect a trend for a forward shift of peak incidence in MD and in line with previous data, MD was found to be generally diagnosed in the fifth to seventh decades of life.
As elaborated in both the general introduction and the first chapter of this thesis, spontaneous episodes of vertigo accompanied by hearing loss, tinnitus and aural fullness are hallmark characteristics in patients suffering from MD. However, since clinical symptoms vary widely and most of these symptoms are subjective and not specific, the disease can present diagnostic challenges and the start of the disease may be hard to assess. Even in the presence of a set of diagnostic criteria, a diagnostic reference standard or confirmatory test is still absent and in case multiple diagnoses causing dizziness coexist this may obscure MD and challenge the physician to clarify the origin of complaints. Moreover, previous research demonstrated that MD commonly coincides with Benign Paroxysmal Positional Vertigo (BPPV [5-7] and psychological distress (PD) [8,9]. To our knowledge, study results presented in chapter 3 were the first to assess the prevalence of second causes of dizziness most common in patients with MD. We found that a second cause of dizziness is common, in about 30% of the MD patients we found a second cause of dizziness. Most commonly this involved BPPV and PD, which together comprised 80% of the second causes.

Strikingly, the prevalence of VM was not as high as one would expect based on previous studies on this matter since VM and MD are commonly associated [10-12]. Based on a cohort study performed by Ghavami *et al.* migraine headaches according to the International Headache Society was found in 51% of the patients and 48% of these patients met the criteria of VM [13]. Due to the fact that our retrospective cohort study started at January 2000 and finished in December 2013 and the vestibular migraine criteria were only published in July 2012, may contributes to the fact the VM criteria were not yet used on a large scale and only registered for a short time frame during the selected study period. Moreover, even before the publication of the VM criteria it would have been of interest to document on the incidence of migraine as it so commonly associated in patients with MD. Unfortunately, this was not registered during the execution of this study. Thus, current results may significantly underestimate the prevalence of VM in our study.

Similar to the research question investigated in chapter 3, chapter 5 also focussed on clinical symptoms. Similar to MD, benign recurrent vertigo (BRV) and vestibular migraine (VM) are characterised by spontaneous attacks of vertigo which both lack a diagnostic reference standard test [14,15].

The diagnostic criteria for definite VM (dVM) describe a patient who experiences spontaneous episodes of vertigo (minimum of five episodes) which are accompanied by migrainous symptoms (i.e. photophobia, phonophobia, unilateral headache) in at least 50% of the episodes. In addition, the patient has migraine or a history of migraine. Either a history of migraine or episodic vertigo accompanied by migrainous symptoms is sufficient for the diagnosis of probable VM (pVM) [16,17,18]. Due to the great similarity between these three diseases, all associated with spontaneous episodes of vertigo, we assessed whether clinical symptoms exist that are clearly distinctive for one of these disorders.

No clinical characteristics could be identified which were distinctive for BRV. Nonetheless, distinctive clinical features were identified for VM and MD. Patients with VM had a clear female preponderance and a positive family history of motion sickness, although the prevalence of motion sickness may be confounded by gender. In addition, vomiting was most common in patients with MD.

With respect to BRV, it remains disputable if this can be a separate identify from either VM or MD. Based on the results found presented in this thesis one cannot conclude this can be seen as a separate identity because information after a preferably long-term follow-up is lacking, ideally monitored without any intervention. This is similar to the complicating factors when diagnosing patients with MD and evaluating their duration of the disease and defining the age of onset of the disease as mentioned in chapter 1. Theoretically, all included patients evaluated in chapter 5 may develop into either VM or MD in case they develop at some point either otologic complaints of migrainous complaints. Moreover, until

this day there is no hypothesis or theory on the pathophysiological mechanism regarding the development of BRV and it remains currently unknown if the disease exists.

Part II

In chapter 6 we assessed the diagnostic accuracy of the vHIT in determining vestibular hypofunction when caloric testing is considered the reference standard in dizzy patients, including patients with MD. In comparison with caloric testing we revealed that the vHIT is a very specific rather than sensitive test for detecting vestibular hypofunction. In case of a normal vHIT, additional caloric testing remains indicated and the vHIT does not replace the caloric test. Nonetheless, based on its high positive predictive value, in case of an abnormal vHIT, additional caloric testing is not necessary.

Chapter 7 evaluated whether the vHIT is more often abnormal in later stages of MD compared to earlier stages. Although the caloric test may be considered as the reference standard for assessing vestibular function, large variability in the results is found in MD, making the test unsuitable to serve as a reference standard [19-21]. Based on previous research in patients with MD we know that caloric test responses decrease most profoundly in the first decade after which responses stabilize at a fixed level of hypofunction of approximately 50% [22-25]. Previous studies evaluating vHIT results in patients with MD when related to the duration of disease, found conflicting results on this matter [26]. Based on the disagreement between pervious study results, we aimed to evaluate whether the vHIT was more often abnormal in patients with a later stage of disease than in those with an early stage, related to either duration of vertigo attacks in years or level of hearing loss. We failed to find a relation between the proportion of abnormal vHIT test results when these were related to stage and duration of disease.

Part III

The final part of this thesis elaborated on the effect of vestibular rehabilitation and betahistine for patients with MD. Moreover, we aimed to identify which treatment previously evaluated by randomised controlled trials, carries the highest efficacy for patients with MD. Chapters 8 to 11 all involved systematic literature searches after which studies were evaluated on their risk of bias, clinical applicability and quality of evidence before translating these findings into their clinical and practical implications.

Although treatment options in MD primarily aim to reduce or control vertigo attacks and to preserve hearing [27-29], the disease also leads to a loss of the vestibular function causing balance problems [30]. Based on the literature review, we found that all studies suffered from a form of bias, low validity and inconsistency of study results. Therefore we concluded that the effect of VR in patients suffering from Menière's disease on balance and dizziness-related quality of life was inconclusive.

Chapter 9 depicts the findings of a systematic review evaluating the effect of betahistine for MD. We found that there was moderate quality of evidence and that there is no effect of betahistine on vertigo when compared to placebo in the treatment of patients with Menière's disease. The evidence suggests that betahistine is generally well tolerated and that the risk of adverse effects is comparable to that of placebo. The quality of the evidence for the reported outcomes in the included studies ranged from very low to moderate. The main focus of future research should be on using comparable outcome measures across studies in order to increase homogeneity and therefore enable data pooling. This could be done by means of patient-reported outcome measures that have been developed and are used in other medical fields. A standardized method of designing and reporting trial results such as the CONSORT statement should be used.
Chapter 11 evaluated the effect of all interventions evaluated in a placebo-controlled designed studies covering: betahistine dihydrochloride, intratympanic injections with gentamicin or steroids, endolymphatic sac surgery and pressure pulse therapy on MD. We concluded that the evidence on the efficacy of interventions for patients with MD is generally of low quality. Based on RCTs with a low risk of bias, there was moderate quality evidence that there is no effect of betahistine and a low quality of evidence for no effect of positive pressure therapy. There is inconclusive evidence with regards to efficacy of intratympanic injections with gentamicin or steroids and endolymphatic surgery. Suggestions for future research are depicted in the last paragraph of this chapter.

CLINICAL RELEVANCE AND IMPLICATIONS

Part I

Based on the finding of chapter 2 and in line with previous research on the age of onset of patients with MD, no progressive increase for a shift in age of onset is expected in MD patients in the Netherlands. Therefore, the clinical implication is that the diagnosis of MD will generally be made between the age of 40 to 69 years and the first presence of symptoms at an older age is uncommon.
The clinical relevance that emerges from chapters 3 and 4, is the need to take PD and BPPV into account when considering therapy options in MD. With respect to PD, cognitive behavioural therapy has shown to be effective to treat dizziness and complaints of tinnitus [29]. In case one is suspecting a psychological disorder associated with the presence of PD, such as an anxiety disorder or depression, this should be diagnosed by means of the criteria and codes of the DSM-V [30]. In case complaints of BPPV are present, this can be effectively treated by means of the canalith repositioning manoeuvres [31].
Although the results of chapter 5 failed to identify clinical characteristics that were distinctive for BRV, patients with VM were significantly more often women with a positive

family history of motion sickness. Vomiting was significantly more often present in patients with MD when compared to BRV or VM. All together the clinical features mentioned may assist the physician in his history taking in a patient with paroxysmal vertigo.

Part II

The findings presented in chapter 6 are useful in daily practice when evaluating patients for vestibular hypofunction. A practical implication of our finding is that the vHIT may be used as a first diagnostic test in determining vestibular hypofunction. An abnormal vHIT is related to significant canal paresis especially when the gain is less than 0.6, and therefore additional caloric testing is not necessary. The advantage of using the vHIT is that it is a simple, safe and non-invasive test that allows repeated testing within a few minutes. Drawbacks of caloric testing are that results may be influenced by skull characteristics, temporal bone circulation, alertness of the patient and previously administered medication [32,33].

The use of the vHIT as a screening tool for vestibular hypofunction is supported by the economic evaluation performed by Rambold *et al.* [34]. This study assessed the optimal diagnostic sequence for the vHIT and the caloric test expressed as the shortest diagnostic time. The diagnostic time was significantly shortened when the vHIT was performed first, even if additional caloric testing was necessary in case of a normal vHIT test result. Based on the time saving aspect it was concluded that starting with the vHIT was the most optimal diagnostic sequence for economic reasons.

With respect to vHIT results in patients with MD in chapter 7, no relation between the duration and stage of disease and the proportion of abnormal vHIT results was found. In case progression of disease is consistently related to an increase of abnormal vHIT results, this could have served as a diagnostic hallmark in the course of the disease.

Part III

Knowledge on the effect of therapy is extremely important since psychological suffering and reduced quality of life are linked to MD, as disabling vertigo attacks can occur without warning [35,36]. The lack of high quality evidence on the effect of VR, intratympanic injections with gentamicin or steroids and endolymphatic sac surgery emphasizes the need for a placebo randomised-controlled designed study which implements a common set of validated subjective and objective outcome measures to clarify if there is evidence for effect. Our study findings implicate that there is moderate quality of evidence that the effect of betahistine and pressure pulse therapy is comparable to placebo. Even though patients may still be motivated to start with therapy, it is questionable whether the initiation of these therapies is justifiable or cost-effective.

Evidence-based step-up therapeutic strategy in MD

Based on our study results following our thorough literature review for effective interventions in MD we would like to elaborate on the clinical implications and propose an evidence-based step-up therapeutic plan for newly diagnosed MD patients.

It is of importance to mention that the primary scientific incentive – the search of finding the truth – may differ from the primary clinical incentive, which is the principle of the will to help and cure a patient. Subsequently, the practical clinical implications of study results may differ from what might be expected from the scientific data, for instance due to ethical reasons. We need to balance between taking scientific results into consideration without losing sight of the ethical perspective.

As mentioned in het discussion section in chapter 11, there is need for homogeneity in study groups, and therefore we recommend to diagnose patients with the internationally defined criteria published by the Bárány society in 2015 [37] by which an objectified low frequency hearing loss is mandatory for the 'definitive' form of MD. Even though these criteria will increase the comparability, it is important other diagnosis are excluded such as vestibular migraine, benign recurrent vertigo, (atypical BPPV), psychological of psychiatric disorder, (superior) semicircular canal dehiscence or genetic disorders such as DFNA9. The initiative for therapy should be based on shared decision making, elaboration on both the potential positive and negative effects.

The first step in treating patients with continuing incapacitating attacks of vertigo would be to start with a three month trail with betahistine hydrochloride three times daily 16 to 24 mg. Although the prescription of betahistine is questionable based on the moderate quality of evidence which implied that placebo was no more effective than betahistine, the incidence of adverse events is rare and treatment with betahistine can be considered to be harmless. The current situation suffers from the absence of any other safe non-invasive effective treatment with high patient acceptability well supported by high quality evidence therefore betahistine still may be considered as a first step in treating MD.

The second step would be to consider the start with intratympanic injections with either steroids or gentamicin. The choice for either medicine should be related to the amount of hearing loss objectified at the time of evaluation.

Generally, the use of intratympanic steroids is recommended, specifically triamcinolone-acetonide (Kenacort), since the permeability of dexamethasone and methylprednisolone appears to be much lower based on recent animal studies [38].

Gentamicin may be proposed especially if intense vertigo attacks prolong in the presence of severe deteriorated hearing loss. Surgical interventions, such as endolymphatic decompression, aiming to preserve hearing should be restricted for only a few selected cases since it is unknown whether these interventions are effective and significant adverse effect may occur [39].

Recently, studies claimed that clipping of the endolymphatic duct blockage is an effective treatment [40]. Unfortunately, results are based on evaluation of the intervention arm only, in other words, without a placebo or sham intervention arm. As mentioned earlier, based on the known placebo effect associated with MD which shows great variety between studies there is no indication for this type of surgery yet. Randomised controlled trials with higher methodological quality are warranted to evaluate if there is a role for this type of surgery in this disease.

Even though it is unknown if vestibular rehabilitation is effective, we feel that MD patients should not be precluded from this type of therapy as it carries the potential of a positive effect and is harmless.

FUTURE RESEARCH AND CONCLUDING REMARKS

During and after conduction of this project, new research questions and hypotheses arose. It would be of great clinical relevance to perform studies to assess these research questions. One of the utmost important issues would be to increase the information available on the natural course of the disease.

It is imperative that the added value of any therapy remains disputable due to lack of knowledge on the natural course of the disease. However, the incapacitating character of the disease makes it unethical to refrain from treatment [38]. Therefore, the information on the natural course of disease is limited, which jeopardises treatment effects in the absence of a placebo.

An online prospective registration system of patients' characteristics may provide relevant information on epidemiological aspects of the disease as well as worldwide use of therapy. Moreover, due to the new set of diagnostic criteria formulated in 2015 [37], future research regarding patients with MD has the ability to significantly increase homogeneity between study populations. Increasing our knowledge on the natural course of disease will not only increase our knowledge on the truly added value of therapy but will also yield great insight in the clinical aspects of the disease related to duration of disease. Moreover, this online prospective registration system may also provide us with information on the function of the vestibular system related to vestibular tests that are performed regularly, preferably including both the caloric test and the vHIT.

Based on the fact that high quality evidence reveals ineffectiveness of betahistine, there is an urgent call for an alternative. We propose that the next randomised controlled trial evaluating the efficacy of therapy in MD should involve intratympanic steroids and preferably include a placebo-arm, low dose and high dose treatment arm to evaluate whether a dose related effect is present.

We strongly recommend the development of outcome measures considered most relevant to patients (patient-reported outcomes) in this field, involving patients, healthcare professionals, researchers, and representatives from the industry to prioritise research. Facilitating future collaborations to recruit adequate sample sizes aiming to significantly increase the quality of evidence in the field of MD.

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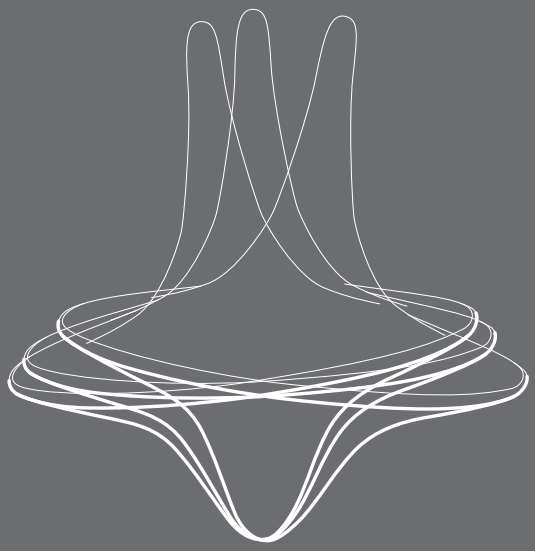

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SUMMARY - SAMENVATTING

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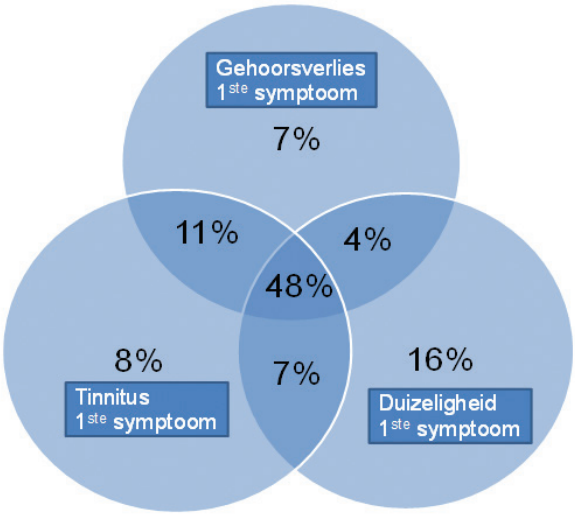
Hoewel het ziektebeeld al in 1861 voor het eerst werd beschreven door de Franse arts Prosper Menière, houdt ook in 2018 de ziekte van Menière onderzoekers nog volop bezig. De ziekte kenmerkt zich door een combinatie van aanvallen van draaiduizeligheid, gehoorverlies, oorsuizen en eventueel een drukgevoel in het oor. Dit proefschrift beschrijft de klinische aspecten, de waarde van aanvullend onderzoek en de effectiviteit van verschillende vormen van therapie bij patiënten met de ziekte van Menière.

Deel I. Klinische aspecten

Zoals eerder genoemd kenmerkt de ziekte van Menière zich in zijn klassieke vorm door spontane aanvallen van draaiduizeligheid welke gepaard gaan met gehoorverlies met name van lage tonen met oorsuizen al dan niet met een sensatie van drukgevoel in het oor. Tot op heden is het pathofysiologische mechanisme voor de ontwikkeling van de ziekte niet bekend. De klinische presentatie in combinatie met een aangetoond gehoorverlies vormt de basis voor het stellen van de diagnose waarbij tot op heden geen diagnostische referentie standaard is ontwikkeld. Doordat zowel de openbaring als het beloop van de ziekte erg variabel is, maakt dit het diagnostisch proces en het bepalen van de effectiviteit van therapie complex. De grote variabiliteit in openbaring van het ziektebeeld wordt geïllustreerd door de volgende figuur:



Figuur 1. Mateijsen, D.J.M. (2001). Definition Menière Groningen: A rational approach to Menière's disease (Proefschrift). Groningen: Rijksuniversiteit Groningen, Chapter 4, Patients and characteristics, pg 31 [1].

Figuur 1 illustreert dat in het merendeel van de gevallen de ziekte van Menière zich niet openbaart met alle klassieke symptomen, maar dat de ziekte regelmatig begint met één of twee symptomen. In voorgaande studies werd het moment waarop de ziekte zich openbaarde gedefinieerd als de start van één van de symptomen als ook de combinatie van het drietal symptomen. Bij het vervolgen van deze patiënten wordt vaak gezien dat uiteindelijk alle symptomen zich openbaren. De periode waarin alle symptomen tot uiting komen kan tussen de maanden tot jaren duren waarover weinig data beschikbaar is. Omdat de openbaring van de ziekte zo variabel kan zijn maakt dit onderzoek doen naar het vóórkomen (epidemiologie) van de ziekte onder de algemene bevolking lastig.
Daarnaast verschillen cijfers over het voorkomen van de ziekte wereldwijd omdat de criteria voor het vaststellen van de diagnose verschillen en deze een aantal keer zijn gereviseerd. Ook verschillen de studies in hun methode en opzet en zijn er ziektebeelden die vergelijkbare klachten kunnen geven, zoals bij vestibulaire migraine, waardoor er overlap ontstaat en dit het differentiëren bemoeilijkt. Al met al is het lastig om in te schatten hoe groot de groep Menière patiënten wereldwijd is. Als we kijken naar de hoeveelheid patiënten gediagnosticeerd met de ziekte van Menière zien we een spreiding tussen de 5 en 150 per 100.000 inwoners op basis van studies die zijn uitgevoerd in de Verenigde Staten, Japan en Europa. In Nederland wordt geschat dat ongeveer 15.000 patiënten lijden aan de ziekte van Menière.

In **Hoofdstuk 2** is gekeken naar de leeftijd van openbaring van de ziekte. Na analyse van 469 Menière patiënten die het specialiseerde duizeligheidscentrum bezochten in de periode 2000 tot 2015, hebben wij bekeken op welke leeftijd patiënten voor het eerst klachten kregen. In recent onderzoek in Japan werd namelijk gesuggereerd dat de ziekte zich de laatste jaren op steeds oudere leeftijd zou presenteren, een significante toename van patiënten die boven de leeftijd van 65 jaar alsnog klachten ontwikkelden.
De resultaten uit ons onderzoek laten deze verschuiving niet zien waarbij wij vonden dat de ziekte zich vooral presenteert tussen het 40^{e} en 69^{e} levensjaar.

Hoe vaak patiënten met de ziekte van Menière een tweede vorm van duizeligheid hebben werd onderzocht in **Hoofdstuk 3**. Het is relevant om te weten of meerdere ziektebeelden naast elkaar spelen om de therapie hierop op aan te passen. Bij bezoek aan het gespecialiseerde duizeligheidscentrum worden er naast een aantal diagnostische onderzoeken ook vragenlijsten ingevuld door patiënten. Onze onderzoeksresultaten hebben aangetoond dat bijna één derde van de gevallen last hebben van een tweede vorm van duizeligheid. De grootste groep werd hierin gevormd door de 'psychologisch distress' (onprettige emotionele en sociale ervaringen uit de aanpassing aan de ziekte) en Benigne Paroxysmale Positie duizeligheid (BPDD, gruis op de verkeerde plek in het

evenwichtsorgaan). Het is belangrijk voor zorgverleners erop bedacht te zijn dat bij Menière patiënten frequent een andere vorm van duizeligheid kan bestaan naast de symptomen van de ziekte van Menière.
Op basis van een prospectieve observationele studie hebben wij gekeken naar drietal verschillende ziektebeelden die alle spontane aanvallen van duizeligheid geven. Wij wilden weten of er een symptoom bestond dat onderscheidend zou zijn voor één van de diagnoses.
Hoofdstuk 5 laat zien dat wij in de periode van januari 2015 tot januari 2017 gegevens hebben verzameld van patiënten met de ziekte van Menière, vestibulaire migraine (VM) en benigne recurrent vestibulopathie (BRV) die ons duizeligheidscentrum bezochten.
Bij VM hebben patiënten aanvallen van duizeligheid zoals bij Menière, dit gaat echter gepaard met klachten van migraine, overgevoeligheid voor licht en/of geluid en aura verschijnselen. Bij BRV hebben patiënten enkel last van spontane duizeligheidsaanvallen zonder klachten van het gehoor of migraine. We hebben geen symptoom kunnen identificeren dat specifiek leek te passen bij BRV. Met behulp van de follow-up van deze studie zal blijken of BRV zich ontwikkelt naar vestibulaire migraine of Menière óf dat het als een apart ziektebeeld beschouwd kan worden.

Deel II. Evaluatie van aanvullend onderzoek
Het tweede deel van het proefschrift gaat over de waarde van de video-head impulse test (vHIT) die gebruikt wordt voor onderzoek naar het functioneren van de halve cirkelvormige kanalen van het evenwichtsorgaan. De vHIT is een vrij nieuwe test waarbij onderzocht kan worden of er sprake is van uitval van halve cirkelvormige kanalen, iets wat regelmatig wordt geobserveerd bij patiënten met de ziekte van Menière.
Jarenlang is calorisch onderzoek de enige manier geweest om het functioneren van het horizontale halve cirkelvormige evenwichtskanaal per kant te kunnen onderzoeken en of er sprake is van uitval. Helaas is de calorimetrie een tijdrovende test en tevens een onaangename stimulus voor de patiënt. Met de v-HIT kan, door middel van snelle, passieve hoofdbewegingen, gekeken worden of de ogen ten tijde van deze hoofdbewegingen goed kunnen blijven fixeren op een doel (bijvoorbeeld een stip op de muur). Indien er sprake is van uitval van als de ogen niet goed kunnen fixeren en een corrigerende oogbeweging wordt gemaakt om opnieuw te fixeren. Door het vastleggen van de oogbewegingen middels een video bril kan dit geobjectiveerd worden.
In **Hoofdstuk 6** tonen wij de resultaten na analyse van 324 patiënten. Uit de resultaten blijkt de vHIT niet een hele gevoelige test te zijn, maar indien de test afwijkend is, er met vrijwel zekerheid geconcludeerd kan worden dat de calorimetrie ook afwijkend zal zijn. Dit betekent voor in de praktijk dat analyse naar uitval van het evenwichtsorgaan tijdbesparend en minder belastend is voor de patiënt om met de vHIT te beginnen. Indien de vHIT

bepaalde uitval aantoont hoeft er geen calorimetrie te volgen. Toont de vHIT wel uitval aan, dan dient er wel calorimetrisch onderzoek uitgevoerd te worden

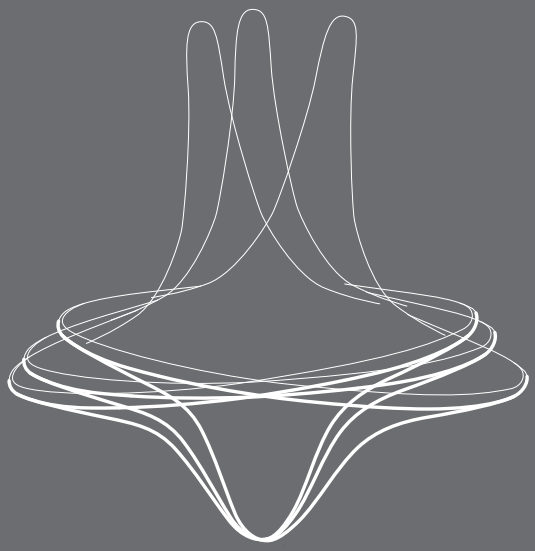
In **Hoofdstuk 7** hebben we onderzocht of de vHIT vaker afwijkend was bij patiënten die al gedurende langere tijd klachten hadden. Op basis van voorgaand onderzoek met de calorimetrie werd bij het vervolgen van het natuurlijk beloop van de ziekte gevonden dat er sprake is van toenemende uitval van het evenwichtsorgaan. Middels evaluatie willen wij achterhalen of deze trend ook terug te zien was in de resultaten van de vHIT. Met andere woorden, is de vHIT, net als de calorimetrie, vaker afwijkend bij patiënten met langdurig klachten?
Bij de evaluatie van 89 Menière patiënten is gekeken naar de duur van de ziekte en de mate van gehoorverlies gecategoriseerd in overeenstemming met criteria die in 1995 zijn opgesteld door de American Academy Otorhinolaryngology Head en Neck Surgery (AAO HNS). Uit de resultaten blijkt dat patiënten met langdurig klachten en een groot gehoorverlies niet significant vaker een abnormale vHIT hebben dan patiënten met kortdurend klachten of weinig gehoorverlies. In dit onderzoek zijn de resultaten gebaseerd op de resultaten van een éénmalig uitgevoerde vHIT waarbij de data retrospectief zijn verzameld. Het is aan te bevelen om bij toekomstig onderzoek patiënten te vervolgen in de tijd waarbij per patiënt de vHIT meermaals herhalen om te kijken of hierin variabiliteit zit en zo aanvullende informatie opgedaan kan worden.

Deel III. Evaluatie van therapie
Het laatste gedeelte van het proefschrift gaat over de behandeling van de ziekte op basis van eerder gepubliceerde literatuurstudies. Tot op heden zijn clinici over de hele wereld nog zoekende naar dé behandeling voor de ziekte van Menière. In **Hoofdstuk 8** hebben wij gekeken naar de effectiviteit van vestibulaire revalidatie, een specifieke vorm van fysiotherapie, welke wordt toegepast voor verschillende vormen van duizeligheid. Vestibulaire revalidatie kan duizeligheidsklachten reduceren, een positief effect hebben op de dagelijkse kwaliteit van leven en angst verminderen. Wij vonden dat tot op heden weinig onderzoek is gedaan de effectiviteit van vestibulaire revalidatie bij patiënten met de ziekte van Menière. Op basis van de relatief slechte kwaliteit van de studies kunnen wij nog geen uitspraak kunnen doen of vestibulaire revalidatie effectief is. Het is onze aanbeveling dat toekomstige studies meer vergelijkbare vestibulaire revalidatieprogramma's gebruiken als ook meer vergelijkbare uitkomstmaten waardoor resultaten van de studies samengevoegd kunnen worden om concreter iets te kunnen zeggen over de grootte van het verwachte effect.

In **Hoofdstuk 9** hebben wij de effectiviteit van betahistine geëvalueerd op basis van een systematische literatuurstudie volgens de methodiek van Cochrane. Gezien de laatste versie van het review dateerde uit 2011, was het opnieuw uitvoeren van de search en een revisie van het protocol gerechtvaardigd. Na data extractie uitgevoerd op 10 gerandomiseerde gecontroleerde trials zijn wij tot de conclusie gekomen dat de studies onderling te veel van elkaar verschilden om een uitspraak te kunnen doen over de grootte van het effect. Behoudens een grote klinische trial, betrof het over het algemeen studies met kleine aantal patiënten van een slechte kwaliteit waardoor er weinig vertrouwen bestond over de correctheid van de gevonden resultaten. De eerdere genoemde grote klinische trial was van goede kwaliteit waaruit volgde dat betahistine niet meer effectief was dan placebo. Gezien de hoge kwaliteit van de studie is het onze aanbeveling om geen betahistine voor te schrijven voor patiënten met de ziekte van Menière, omdat betahistine gebleken ineffectief is en wel bijwerkingen kan geven.
In **Hoofdstuk 10** beschrijven wij de methodiek die we gaan gebruiken om een systematisch literatuur onderzoek te verrichten naar alle gerandomiseerde placebogecontroleerde studies die op het gebied van effectiviteit van de ziekte van Menière zijn gepubliceerd.
De resultaten in **Hoofdstuk 11** tonen aan dat wij na literatuuronderzoek uiteindelijk 23 gerandomiseerde placebogecontroleerde studies hebben gevonden welke naar de effectiviteit van vijf verschillende therapieën hebben gekeken, zijnde: (1) betahistine, (2) intratympanale injecties met (3) gentamicine of (3) dexamethason, (4) 'positive pressure pulse' therapie (of) en (5) chirurgie. Op basis van de resultaten komen wij tot de conclusie dat zowel betahistine als 'positive pressure pulse' therapie niet effectief zijn voor de ziekte van Menière. Tot op heden blijkt het inconclusief of intratympanale injecties met gentamicine of dexamethason of chirurgie effectief zijn voor de patiënten met de ziekte van Menière gezien de slechte kwaliteit van de methodiek.

Belangrijkste conclusies en aanbevelingen
Dit proefschrift beschrijft de klinische aspecten van de ziekte van Menière, de waarde van de vHIT bij onderzoek naar eenzijdige vestibulaire uitval als ook de resultaten wanneer deze worden gerelateerd naar de ziekteduur en de mate van gehoorverlies.
Wij bevelen aan dat toekomstige studies een placebogecontroleerde opzet gebruiken, waarbij in het geval van intratympanale injecties overwogen kan worden om een dosis-respons relatie te evalueren door verschillende dosering met elkaar te vergelijken. Daarnaast is tot op heden nog veel onduidelijk over het natuurlijk beloop van de ziekte wat resulteert in onduidelijkheid over de daadwerkelijke meerwaarde van therapie. Een prospectieve online registratie van gegevens bij patiënten met de ziekte van Menière zou niet alleen veel informatie bieden over het natuurlijk beloop maar ook ten aanzien van epidemiologische karakteristieken van de ziekte. Naast gebruik van de recent gepubliceerde internationale

criteria is het van belang dat studies vergelijkbare uitkomstmaten gebruiken zodat de onderlinge vergelijkbaarheid wordt vergroot, en dat de kwaliteit van studies significant wordt vergroot.



A

APPENDICES

ABBREVIATIONS

LIST OF CONTRIBUTING AUTHORS

LIST OF PUBLICATIONS

CURRICULUM VITAE

ABBREVIATIONS

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
ABC	Activities Balance Confidence
ADC	Apeldoorn Dizziness Centre
BPPV	Benign Paroxysmal Positional Vertigo
BRV	Benign Recurrent Vestibulopathy
BRU	Balance Rehabilitation Unit
CI	Confidence Intervals
CENTRAL	Cochrane Central Register of Controlled Trials
CPD	Computerized Dynamic Posturography
dVM	definite Vestibular Migraine
DP	Directional Preponderance
DHI	Dizziness Handicap Inventory
DGI	Dynamic Gait Index
FI	Fletcher Index
HADS	Hospital Anxiety and Depression Scale
HVPT	Hyperventilation Provocation Test
HVS	Hyperventilation syndrome
JSER	Japanese Society for Equilibrium Research
LOS	Limits of Stability
MRI	Magnetic Resonance Imaging
MD	Menière's disease
NPV	Negative Predictive Value
NQ	Nijmegen Questionnaire
PD	Psychological Distress
PTA	Pure Tone Audiometry
VM	Vestibular Migraine
pVM	probable Vestibular Migraine
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomised controlled trials
SOT	Sensory Organization Test
STARD	Standards for Reporting of Diagnostic Accuracy Studies
SPSS	Statistical Package for the Social Sciences
VP	Vestibular Preponderance
VR	Vestibular Rehabilitation
vHIT	video-Head Impulse Test
VOR	Vestibular Ocular Reflex

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CURRICULUM VITAE

Babette Fiebke van Esch werd op 8 september 1987 geboren in Eindhoven. In 2006 behaalde zij haar vwo-diploma aan het St. Bonifatiuscollege in Utrecht. In hetzelfde jaar startte zij met haar studie geneeskunde aan het Universitair Medisch Centrum Utrecht waarbij zij in 2013 haar opleiding afrondde. Na afronding van haar studie geneeskunde heeft zij gewerkt als docent anatomie waarbij zij de Basis Kwalificatie Onderwijs heeft behaald. Hierna deed zij klinische ervaring op bij de cardiothoracale chirurgie in het UMC Utrecht. Vanaf november 2014 tot en met december 2016 deed zij wetenschappelijk onderzoek bij het Apeldoorns Duizeligheidscentrum. Per 1 januari 2017 is zij begonnen met de KNO-opleiding in het Leids Universitair Medisch Centrum.

Babette Fiebke van Esch was born on 8 September 1987, in Eindhoven, The Netherlands. In 2006 she completed her secondary education (vwo) at the St. Bonifatiuscollege in Utrecht. In the same year she started studying medicine at the University Medical Centre (UMC) Utrecht . In 2013 she obtained the master degree in Medicine. After completing her medical school, she started as a junior teach in anatomy department at the UMC Utrecht. In this period she obtained the Basis Kwalificatie Onderwijs (BKO). Subsequently, she worked at the cardiothoracic surgery department at the UMC Utrecht before she started as a full-time PhD student at the Apeldoorn Dizziness Centre in Apeldoorn in November 2014 through December 2016. In the beginning of 2017 she entered as a clinical resident at the department of Otorhinolaryngology at the Leids University Medical Centre.