Vertiginous Episodes in Menière Disease following Transmyringeal Ventilation Tube Insertion: A Systematic Review on the Current State of Evidence

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Abstract

Introduction Menière disease (MD) is a disorder characterized by episodes of vertigo, sensorineural hearing loss, tinnitus and aural fullness.

Objectives To assess the effect of ventilation tube insertion (VTI) on vertiginous episodes in patients ($\geq$ 18 years old) with MD.

Data Synthesis A systematic literature search on randomized clinical trials (RCTs), nonrandomized trials and other systematic reviews was performed. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to assess the overall certainty of evidence.

Two RCTs and four nonrandomized studies were identified. Data extraction was only possible for one RCT. Results showed that the number of patients with no vertigo attacks significantly increased following active treatment (relative risk 1.52; [95% confidence interval: 1.19–1.94]). The quality of evidence was rated as low. None of the nonrandomized trials included a proper control group, which hindered data extraction and quality assessment.

Conclusion There are currently no RCTs that specifically assess the efficacy of VTI in patients with MD. Current limited data suggest a considerable positive effect on the number of vertiginous episodes in patients with MD. However, due to poor evidence, a fluctuating course and a substantial placebo-effect associated with MD-treatment, no solid conclusion (s) regarding the efficacy of VTI can be made. There is a need for high-quality RCTs.

Keywords
► ventilation tube insertion
► Meniere disease
► vertigo
► dizziness
► hearing

Introduction

Menière disease (MD) is an idiopathic disorder characterized by recurrent episodes of vertigo, unilateral sensorineural hearing loss, tinnitus, and aural fullness.[1] The occurrence of MD varies according to applied diagnostic criteria, geographic area, and sources of data. This is accentuated in the prevalence of MD, which ranges from 513 per 100,000 inhabitants in Finland to 3.5 per 100,000 inhabitants in Japan.[1]

Several classification criteria of MD have been formulated over time. The most used are likely the criteria jointly formulated by the Classification Committee of the Bárány Society, The Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology (EAONO), the Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) and the Korean Balance Society from 2015, and the criteria formulated by the American Academy of Otolaryngology – Head, and Neck Surgery (AAO-HNS) in 1995.

The first mentioned criteria from 2015[2] include two categories: definite and probable MD. Definite MD is defined as a chronic inner-ear disorder presenting with:

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

In probable MD, the same diagnostic criteria must be fulfilled with two exceptions according to the Bárány Society. A history of a permanent or fluctuating sensorineural hearing loss is sufficient, documentation of hearing loss is not required (see **b** above), and the episodes of vertigo or dizziness may last from 20 minutes to 24 hours.[2]

The criteria of MD formulated by the AAO-HNS in 1995 includes four categories: certain, definite, probable, and possible MD.

Certain MD:
• Definite MD plus histopathological confirmation.

Definite MD:
• Two or more definitive spontaneous episodes of vertigo lasting 20 minutes or longer
• Audiometrically documented hearing loss on at least one occasion
• Tinnitus or aural fullness in the treated ear
• Other causes excluded

Probable MD:
• One definitive episode of vertigo
• Audiometrically documented hearing loss on at least one occasion
• Tinnitus or aural fullness in the treated ear
• Other causes excluded

Possible MD:
• Episodic vertigo without documented hearing loss OR
• Sensorineural hearing loss fluctuating or fixed with disequilibrium but without definitive episodes
• Other causes excluded

There is a variety of treatment options for MD, ranging from dietary modifications to medication to surgery.[3,4] However, there is a lack of consensus on which treatment options to choose.[1]

Transmyringeal ventilation tube insertion (VTI) has been suggested as a treatment option in MD. The first to suggest VTI was Tumarkin in his paper from 1966.[5] He suggested that poor tubal function and negative middle-ear pressure were associated with MD. His suggestion was later supported by Lall.[6] In 1975, Cinnamond stated that eustachian tube dysfunction (ETD) was not a consistent feature of MD and that treatment with VTI was futile.[7] This was also supported by Hall et al.[8] However, in 1988, Montandon et al decided to reintroduce VTI as a treatment option. They found that the insertion of a ventilation tube prevented occurrence of vertiginous attacks in 82% of 28 patients suffering from MD with incapacitating vertigo resistant to medical treatment.[9]

Ventilation tube insertion is a swift and relatively safe procedure and is therefore suggested as one of the early treatment options in MD in countries such as Denmark and Norway.[10,11] Tube insertion in adults is usually easily performed as a procedure under local anesthesia. The main complications from VTI are purulent otitis media while the tube is in place and persistent perforation following tube extrusion.

The primary aim of the present study was to assess the potential effect of VTI on vertiginous episodes in patients with MD by reviewing the current literature; the second aim was to assess potential effects of VTI on hearing, its impact on daily life, as well as serious adverse events.

Review of Literature

The present systematic review is based on principles described in the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[12] and in accordance with the guidelines of the Cochrane Collaboration and Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA).[13] The study protocol was registered in PROSPERO (Registration number: CRD42019134851, Acceptance date: 8th of July, 2019) and structured in accordance with the Population, Intervention, Comparison, and Outcome (PICO) framework,[14] from which literature was selected accordingly. The present review is part of a larger guideline on MD published by the Danish Health Authority in 2018.

Search Strategy

We performed a literature search in the electronic bibliographic databases MEDLINE, EMBASE via Ovid, and PsycINFO. The search strategy contained terms relating to or describing the intervention. The search strategy was developed using medical subject heading (MeSH) and text words related to our eligibility criteria. The language was restricted to English, Danish,

Swedish, and Norwegian. There were no publication year restrictions. We searched for relevant randomized controlled trials (RCTs), other systematic reviews, and nonrandomized trials assessing the effect of VTI compared with placebo or no intervention in patients with MD. The last search date was May 2019. The search protocols are provided in the supplementary information.

Study Selection and Data Extraction

Title and abstract of all search hits were assessed by two reviewers, independently. Assessment of the studies included study settings, population demographics and baseline characteristics, details on intervention and control conditions, study design, outcome, and time of measurement.

Two authors independently performed the data extraction and risk of bias assessment. Any discrepancies were resolved through discussion among all authors. Only data available in the respective studies were used. The authors of the included studies were not contacted for further information.

Population

The inclusion criteria consisted of studies including patients aged $\geq$ 18 years old, with definite or probable MD as defined by Bárány Society 2015[2] or the American Academy of Otolaryngology – Head, and Neck Surgery (AAO-HNS) criteria from 1995.[15] The exclusion criteria included patients with a vertigo-related diagnosis other than MD and studies including patients with MD that did not use the appropriate diagnostic criteria.

Intervention and Comparison

The intervention included transmyringeal VTI. Patients using a placebo device, or no intervention served as a control group.

Outcome

The primary outcome measures were the frequency of vertiginous episodes and number of patients with serious adverse events assessed at a minimum of 1 month following the initial treatment.

Secondary outcomes were assessed at a minimum of 1 month following the initial treatment. Secondary outcomes included:

1. Severity of vertigo: Measured by vertigo score
2. Frequency of vertigo: Number of days with vertigo attacks
3. Hearing loss: Proportion of patients with progression in hearing loss, audiometrically documented by standard pure-tone and speech audiograms
4. Tinnitus: Proportion of patients with a reduction of subjective tinnitus, measured by questionnaires such as Tinnitus Handicap Index (THI) or others
5. Quality of life: Proportion of patients with an increase of quality of life measured by patient-reported questionnaires such as the Short Form[16] Health survey (SF-36) or others
6. Impact on daily life: Proportion of patients with an increase of daily functioning as measured by the Dizziness Handicap Inventory (DHI) questionnaire.

Critical Appraisal

We planned to assess the quality of any included systematic reviews by using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool,[17] whereas individual RCTs were assessed using the Cochrane risk of bias tool[18] by evaluating the risk of inadequate patient allocation and concealment, blinding of patients, personnel and outcome assessors, attrition of data, selective outcome reporting and other types of bias. We planned to assess nonrandomized trials using the ROBINS-I tool.

Data Synthesis and Overall Certainty of Evidence

For dichotomous outcomes, we calculated relative risk alongside a 95% confidence interval [CI]. The effect size of continuous outcomes was assessed as mean difference including a 95% CI. If applicable, statistical heterogeneity would be calculated using I2 statistics, and based on the level of heterogeneity, either a fixed-effect or random-effect model would be applied.[19–21] The analyses and forest plots were produced in the Review Manager Software (version 5.2) (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).[22]

We assessed the certainty of evidence using the GRADE approach.[12] Here, the overall quality of evidence would be based on the lowest quality of the primary outcomes. The overall certainty of evidence could range from high, moderate, low, and very low.[12] All findings were summarized in a summary of findings table.

Results

We did not find any systematic reviews that matched our inclusion criteria. The systematic search identified four nonrandomized trials[23–26] (►**Table 1**) and two RCTs [27,28] (►**Table 2**).

Study Characteristics

The patients included in all of the studies were diagnosed according to the diagnostic criteria from AAO-HNS 1995. In all studies, the intervention was treatment with a VTI. However, in the studies by Russo et al[28] and Barbara et al,[26] a part of the study-group proceeded to the next phase of the trial, which was treatment with a Meniett device. The age-range was not mentioned in the studies by Russo et al[28] and Kitahara et al,[27] but the mean age of the VTI-groups was 52 and 46.7 years old, respectively. The population in the rest of the included studies consisted of patients in the age range between 26 and 77 years old.

Barbara et al[26] conducted a trial with 20 MD patients having a VTI placed for 20 days followed by additional treatment with a Meniett device.

Sugawara et al studied seven patients with MD having a VTI. In 3 of the 7 patients, the VTI remained in place for 42 months. In the other four cases, the tubes were extruded spontaneously within 2 years.[23]

In the study by Park et al,[24] 24 patients with MD had a VTI. The patients also had an ipsilateral middle ear pressure $< - 50$ daPa.

Table 1 Observational studies

Author	Patients	1st follow-up	2nd follow-up	Vertigo-score (1st follow-up)	Vertigo-score (2nd follow-up)	Before/after comparison
Barbara et al*	20	20 days	–	90% with positive effect in terms of absence (50%) or marked reduction (40%).	–	Mean episodes of vertigo in the 2 months before treatment with VTI: 9.22 Mean episodes of vertigo during the 20 days with VTI: 1.27
Sugawara et al[23,26]	7	24 months	42 months	Number of patients in defined groups***: Complete: $n = 0$ (0%) Substantial: $n = 5$ (71%) Limited: $n = 1$ (14%) Insignificant: $n = 1$ (14%) Worse: $n = 0$ (0%)	Number of patients in defined groups***: Complete: $n = 0$ (0%) Substantial: $n = 4$ (57%) Limited: $n = 3$ (43%) Insignificant: $n = 0$ (0%) Worse: $n = 0$ (0%)	
Park et al**	24	6 to 26 months	–	No complaints: 9% Improvement: 59% No change after VTI: 31%.	–	Complete control-group: 1.5 vertigo episodes per week before VTI, 0 after VTI. Improvement-group: 7.8 episodes per week before VTI, 4.2 after VTI. No change-group: 4.1 episodes before VTI, 3.9 after VTI.
Ogawa et al[24,25]	15	12 months	24 months	Number of patients in defined groups***: Complete: $n = 3$ (20%) Substantial: $n = 7$ (47%) Limited: $n = 2$ (13%) $n = 3$ (20%) required other treatments.	Number of patients in defined groups***: Complete: $n = 7$ (47%) Substantial: $n = 3$ (20%) Limited: $n = 1$ (7%) $n = 4$ (27%) required other treatments, of which 1 required intra-tympanic gentamicin 15 months after VTI.	

Abbreviation: VTI, ventilation tube insertion.

*The studies were conducted for examining the effect of a positive pressure device. The stated numbers are from the preliminary phase between VTI and the initiation of positive pressure treatment.

**Classifying the change of symptoms after surgery according to AAO-HNS resulted in 9% of patients in class A, 23% in class B and 36% in class C. The remaining 31% represented class D.

***A numeric value was calculated as the average number of definitive spells per month during VTI divided by the average vertigo spells in the months before treatment multiplied by 100. Patient response was grouped into: complete = 0, substantial = 1–40, limited = 41–80, insignificant = 81–120, and worse = > 120.

Table 2 Randomized studies

Author	Patients	1st follow-up	2nd follow-up	Vertigo-score (1st follow-up)
Russo et al*	129	Mean 35 days	–	Of the 129 patients who received ventilation tube, 32 patients (25%) experienced no vertigo in the preliminary phase (1st follow-up). In the remaining 97 patients, the mean number of vertigo episodes decreased from 4.3 to 2.6 and from 3.2 to 2.5 in patients scheduled for later placebo- and intervention treatment, respectively.
Kitahara et al**	Group 1: 70 Group 2: 70 Group 3: 63 Group 4: 60	24 months	–	Complete control for the last half a year was found in: Group 1 (control): 54% Group 2 (abundant water intake): 81.4% Group 3 (VTI): 84.1% Group 4 (sleeping in darkness): 80%

Abbreviation: VTI, ventilation tube insertion.

*The study examined the effect of a positive pressure device. The presented numbers in the table are from the preliminary phase from after VTI but before initiation of positive pressure treatment.

**The effect of 3 different interventions was studied, of which placement of a ventilation tube in the tympanic membrane was one.
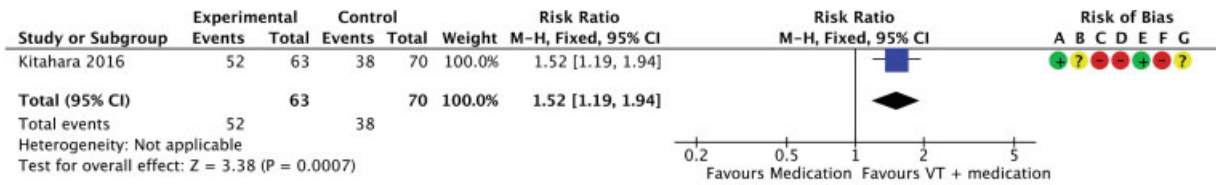
Fig. 1 Number of patients with no vertigo attacks two years after treatment with VTI and medication compared with medication alone. Results are reported as risk ratio (RR) with a 95% confidence interval.

Ogawa et al[25] conducted a trial with 15 patients with MD having a VTI. They used the same control of vertigo by numeric value as Sugawara et al.[23]

Kitahara et al[27] studied the effect of different interventions to decrease the production of the stress hormone vasopressin in patients with MD. One of the interventions (group III) was the placement of a ventilation tube in the tympanic membrane, and 70 patients were included.

In the study by Russo et al,[28] 129 patients with MD were included. The study was divided into two phases. The first phase comprised of insertion of a ventilation tube followed by an 8-week interval with concomitant registration of the number of vertiginous episodes. The second phase was treatment with a Meniett device.

Data Synthesis

The study by Kitahara et al[27] was the only RCT that enabled data extraction and risk of bias assessment. The study design of the included nonrandomized controlled trials hindered data extraction and subsequent quality assessment using the ROBINS-I tool.

Primary Outcomes

Frequency of Vertigo Attacks

Kitahara et al[27] investigated the effect of VTI on the number of patients with no vertigo attacks following 2 years of

treatment. In the study, two groups were compared. Group 1 was treated with VTI and medication (medication consisted of either diuretic, betahistine, diphenidol, dimenhydrinate, or diazepam) and consisted of 63 patients. Group 2 was treated with medication only (diuretics, betahistine, diphenidol, dimenhydrinate, or diazepam) and consisted of 70 patients. The results showed that the number of patients with no vertigo attacks improved following concomitant treatment with VTI (RR 1.52; 95%CI: 1.19–1.94) (►**Fig. 1**).
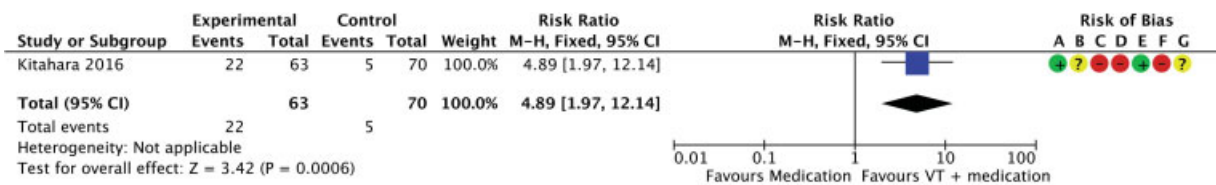
Secondary Outcomes

Hearing

Kitahara et al[27] investigated the effect of VTI and medication on the number of patients with improved hearing after 2 years of treatment (group 1) compared with the medication-only group (group 2). Results showed that the number of patients with improved hearing (i.e., better by ≥ 10 dB) increased following treatment with VTI (RR 4.89; 95%CI: 1.97–12.14) (►**Fig. 2**).

Impact on Daily Life

Kitahara et al[27] also assessed the impact on daily life, as indicated by the degree of stress (measured using the stress response scale-18),[29] after 2 years of treatment with VTI and medication (group 1), compared with medication alone (group 2). Results showed no effect on the degree of stress

Fig. 2 The effect of VTI and medication on the number of patients with improved hearing after 2 years of treatment. Results are obtained as relative risk and the accompanying 95% confidence interval. The direction of the effect is shown on the right, as either favoring VTI and medication or medication alone.

Fig. 3 The effect of VTI and medication on Impact on daily life (degree of stress) after two years of treatment. Results are obtained as mean difference (MD) and the accompanying 95% confidence interval. The direction of the effect is shown on the right, as either favoring VTI and medication or medication alone.
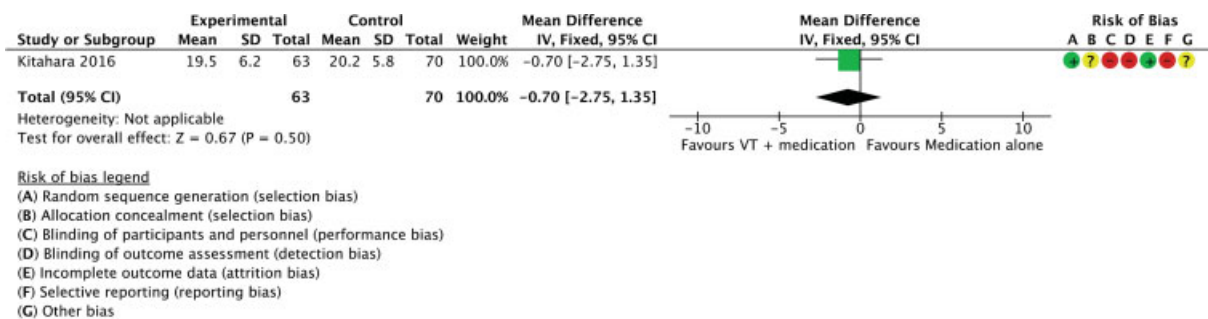
following treatment (mean difference (MD) 0.70; 95%CI -1.35–2.75).

In our protocol, we included serious adverse events as a primary outcome and quality of life and tinnitus as secondary outcomes. None of these parameters were evaluated in the study by Kitahara et al[27] (►**Fig. 3**).

Risk of Bias

In Kitahara et al,[27] there was a low risk of bias for allocation sequence generation, as the method applied was considered sufficient. The allocation concealment was unclear due to inadequate description. Blinding of both participants, personnel, and outcome assessors were a high risk of bias. The risk of bias concerning incomplete outcome data was low. Selective outcome reporting was high. There was no indication of other sources of bias.

Certainty of Evidence (GRADE)

For both the primary and secondary outcomes, the quality of evidence was low due to serious risk of bias and serious imprecision. In accordance with GRADE, the overall quality of evidence is based on the primary outcome, in which the overall quality was very low.

Discussion

We found no RCTs that directly assessed the effect of VTI compared with placebo or no intervention in patients with MD. At first glance, the effect of ventilation tubes seems to decrease the number of vertiginous episodes in MD patients. However, the certainty of the evidence is questionable, as data are based on one randomized trial and four nonrandomized trials, in which quality assessment was not possible. In addition, the placebo effect(s) associated with MD treatment is generally considered to be substantial, which also should be taken into account when evaluating the results. Furthermore, in a retrospective study, Silverstein found that 57% of patients no longer experienced any vertiginous attacks 2 years after the inclusion without any kind of surgery.[30] This underscores the importance of the use of a placebo-group when studying the effect of any treatment in MD.

Perception of aural fullness is another symptom of MD. The number of studies investigating aural fullness is sparse because aural fullness is often considered a lesser complaint compared with the triad of vertigo, tinnitus, and hearing loss, as it is usually less debilitating. Nonetheless, aural fullness can be extremely upsetting to some patients. In a review by Sevilla et al, they aimed to catalog data on the use of VTI for aural fullness in MD. They included five studies, of which three studies showed no significant changes in aural fullness. However, the remaining studies showed an effect of VTI on aural fullness. In one of the studies, the authors stated that 6 of 7 patients experienced relief of aural fullness. In the other study, the authors stated that 66 percent showed relief. Sevilla et al concluded that there is a paucity of evidence investigating VTI on aural fullness in MD.[31]

The pathophysiology of MD is not fully understood. In human temporal bone studies, MD symptoms have been associated with accumulation of endolymph within the scala media and the sacculus, referred to as endolymphatic hydrops (EH).[1] Many suggestions for the development of EH have been proposed, including blockage of the endolymphatic flow, blockage of the cochlear or vestibular aqueducts, ETD, and reduced regulation of vasopressin-secretion.[27,32–35]

The association between MD and ETD has been proposed in several articles.[5] However, data from studies on MD and ETD are contradictory. Most of the studies that examined the eustachian tube in MD patients used indirect methods such as tympanometry alone or in combination with whole-body pressure chambers. However, normal tympanometric measures of the middle-ear do not necessarily reveal mild hypo- or dysfunction of the eustachian tube.[35] Park et al used sonotubometry in their study as it allows detection of a mild hypo- or dysfunction by direct evaluation of the eustachian tube function. They found that patients with MD often have a mild, bilateral ETD.[35]

A possible consequence of blockage of the eustachian tube is the development of negative pressure and/or low oxygen tension in the middle ear cavity. This will also affect the oxygen tension in the perilymph, which is normally transmitted through the round window membrane.[36] In addition, a negative middle ear pressure might change the position of the round window membrane resulting in a decrease of the pressure-release-mechanism in the inner ear, normally transmitted through the cochlear aqueduct to the cerebrospinal fluid.

Under normal circumstances, the patency of the cochlear aqueduct is a key factor in intracochlear hydromechanics. If the cochlear aqueduct is blocked, the cerebrospinal fluid cannot provide the reference pressure for the perilymph and, to a large extent, the endolymph.[16] Therefore, as the patency of the cochlear aqueduct decreases with increasing perilymph pressure as a possible result, endolymph pressure may also increase.[24] However, other factors may contribute to the development of MD, as not every patient with a negative middle-ear pressure develops MD. Hence, it is plausible that an abnormality in either the endolymphatic duct and/or in the cochlear or vestibular aqueduct may predispose to the development of MD, and ETD may further aggravate the EH resulting in clinical symptoms of MD.[23]

A ventilation tube equalizes the pressure gradient between the outer and middle ear. Hypothetically, as middle-ear-pressure approaches outer ear pressure following VTI, the abnormally positioned round window membrane may reverse to its original place, increasing the patency of the cochlear aqueduct within the inner ear and normalizing the perilymphatic pressure. The oxygen-tension in the middle- and inner ear may also increase. Eventually, this may lead to normalization of the perilymphatic pressure as well as endolymphatic pressure, as the Reissner membrane can only withstand a relatively small pressure differential between the two chambers.[16] This can theoretically lead to remission of MD symptoms.

Besides, VTI has been proposed to modify the vasopressin-secretion from the hypothalamic-pituitary system mediated by vestibulo-hypothalamic neural interactions.[27]

Final Comments
There are no RCTs that directly assess the efficacy of VTI on the number of vertiginous attacks in patients with definite or probable MD. Current data are suggestive of a considerable positive effect on the number of vertiginous attacks in patients with MD. However, due to poor quality data, the fluctuating course, and a substantial placebo effect associated with MD treatment, no solid conclusion(s) regarding the efficacy of VTI in patients with MD can be made. There is a need for high-quality RCTs on this matter.

Trial Registration Number
The protocol for the manuscript is registered in PROSPERO. Registration number: CRD42019134851, acceptance date: July 8, 2019. The present review was performed in accordance with the guidelines for systematic reviews and meta-analyses and Preferred Reported Items for Systemtic Reviews and Meta-analyses (PRISMA).

Conflicts of Interest
The authors have no conflicts of interest to declare.

Acknowledgment

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