The Laryngoscope

Treatment of Vestibular Migraine: A Systematic Review and Meta-analysis

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Objective: To assess the efficacy of the various therapies used for the prevention of vestibular migraine (VM).

Methods: Primary studies were identified though PubMed, Scopus, PsycINFO, and Cochrane Library by two independent investigators for articles published through April 2019. The search identified randomized comparison or observational studies pertaining to vestibular migraine treatment. Meta-analysis was performed on pre- and posttreatment Dizziness Handicap Inventory, vertigo frequency, and percentage of perceived improvement.

Results: Literature search identified 13 studies that reported sufficient outcome measures to be included in the analysis. Patients with VM had a mean age of 43.3 years with female-to-male gender ratio of 2.1:1. Classes of therapeutic agents included antiepileptic drugs, calcium channel blockers, tricyclic antidepressants, β-blockers, serotonin and norepinephrine reuptake inhibitors, and vestibular rehabilitation. All treatment options that were analyzed demonstrated improvement in all of the outcome parameters, but due to significant heterogeneity and lack of standardized reporting on outcomes, establishment of preferred treatment modality could not be determined.

Conclusions: Various treatment modalities have been evaluated for preventative treatment of VM. Physician familiarity, patient comorbidities, and the side-effect profiles of various interventions likely influence the selection of intervention. Future randomized controlled trials with restrictive inclusion criteria and generalizable standardized outcome measures will allow for more robust meta-analyses and for more evidence-based treatment of vestibular migraines.

Key Words: Vestibular migraine, treatment, vertigo, migraine, dizziness, headache.

***Laryngoscope*, 00:1–9, 2020**

INTRODUCTION

Vestibular migraine (VM) is a common cause of episodic vertigo that accompanies migraine headache. In a recent population-based survey in the United States, VM was prevalent in 2.7% of adults and was found to be the most common cause of episodic dizziness in adults.[1] Despite its relatively high prevalence, VM still remains an underdiagnosed entity.[2,3] This high prevalence of a disabling disorder creates a significant burden in healthcare and draws attention to the need for effective treatment options.

The diagnostic criterion for definite and probable VM has been proposed by Neuhauser et al.[4] and was later revised by the Bárány Society and the International Headache Society (IHS) in a consensus statement to be recognized as an unique entity.[5] The diagnosis is contingent on the clinical description of the symptoms reported by the patients and the exclusion of other potential secondary causes by appropriate investigation (Table I). Several terms have been previously used to describe vestibular migraine, including vestibular migraine, migrainous vertigo, migraine-associated vertigo, migraine-associated dizziness, and migraine-related vestibulopathy. Diagnosing vestibular migraine is challenging, as there is no established confirmatory diagnostic test or biomarker for the disorder. It is further complicated by the fact that dizziness and vestibular symptoms are altogether prevalent in patients suffering from migraine.[6] Otogenic causes of vestibular symptoms may include disorders such as benign paroxysmal positional vertigo and Meniere's disease, which are part of the differential diagnosis for these patients.

The underlying pathophysiology of vestibular migraine is poorly understood, and most of the current hypotheses are based on the knowledge of migraine. The response to antimigraine therapy suggests headache and dizziness may share a common etiology in this patient population.[7] It has been suggested that reciprocal connections between brainstem vestibular nuclei and the structures that modulate trigeminal nociceptive inputs may be involved in the pathogenesis of VM.[2] Some neurotransmitters involved in the pathogenesis of migraine (e.g., serotonin, noradrenaline, and dopamine) may be involved in the pathogenesis of VM and influence treatment options for VM.[8–10]

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Additional supporting information may be found in the online version of this article.

Editor's Note: This Manuscript was accepted for publication on January 10, 2020.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.28546

TABLE I.
Vestibular Migraine Criteria.

Neuhauser 2001 Vestibular Migraine
1. Recurrent vestibular symptoms (rotatory/positional vertigo, other illusory self or object motion, head motion intolerance) of at least moderate severity
2. Migraine according to International Headache Society criteria
3. At least one of the following migrainous symptoms during at least two vertiginous attacks: migrainous headache, photophobia, phonophobia, visual or other auras
4. Other causes ruled out by appropriate investigations

2012 Consensus Criteria of the Bárány Society and the International Headache Society	
Vestibular Migraine	Probable Vestibular Migraine
A. At least five episodes of vestibular symptoms of moderate to severe intensity lasting 5 minutes to 72 hours	A. At least five episodes of vestibular symptoms of moderate to severe intensity lasting 5 minutes to 72 hours
B. Current or previous history of migraine ± aura according to the ICHD	B. Only one of the criteria B or C for vestibular migraine is fulfilled
C. One or more migraine features with at least 50% of the vestibular episodes	C. Not better accounted for by another vestibular or ICHD diagnosis
D. Not better accounted for by another vestibular or ICHD diagnosis	

Vestibular symptom: spontaneous vertigo; positional vertigo, visually-induced vertigo; head motion-induced vertigo; head motion-induced dizziness with nausea.

Migraine features: visual aura, photophobia, phonophobia, and/or headache with at least two distinct features (e.g., one-sided location, moderate-to-severe pain intensity, aggravation by routine physical activity, pulsating quality).

ICHD = International Classification of Headache Disorders.

Unfortunately, there are no existing guidelines for the treatment of VM. As such, typical abortive treatments as well as prophylactic medications for classic migraine have been adopted to treat VM.[11–14] However, the evidence of treating VM with antimigraine medication is lacking, as most current investigations are uncontrolled cases series with retrospective design or observational studies.[15] Pharmacologic agents commonly used for prophylaxis include β-blockers (e.g., propranolol, bisoprolol, metoprolol), calcium channel blockers (e.g., verapamil, amlodipine, flunarizine, cinnarizine), antiepileptic drugs (e.g., valproic acid, lamotrigine), and tricyclic antidepressants (e.g., amitriptyline, nortriptyline). In the absence of evidence-based standardized treatment protocols, therapeutic approaches are often determined by physician familiarity and preference. In an effort to better understand the role of prophylactic treatment for vestibular migraine, the present study aimed to 1) review the existing scientific literature on the prophylactic treatment for vestibular migraine and 2) perform a meta-analysis on available data to elucidate any possible therapeutic advantage.

MATERIALS AND METHODS

Data Collection and Selection

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] To identify studies for inclusion, a research librarian (E.B.) with expertise in conducting systematic reviews developed detailed search strategies in the following four databases: PubMed (National Library of Medicine, National Institutes of Health), Scopus (Elsevier), PsycINFO (EBSCO), and Cochrane Library (Wiley). The search strategies used a combination of subject headings (e.g., Medical Subject Headings [MeSH] in PubMed) and keywords for the following three concepts: migraine disorders, vestibular diseases, and patient-reported outcomes or pharmacologic treatments. The PubMed search strategy was modified for the other three databases, replacing MeSH terms with appropriate subject headings, when available, and maintaining similar keywords. The search strategies for each database are detailed in Supporting Appendix 1. The databases were searched from inception through April 22, 2019, and results were limited to English language only. To identify additional articles, the reference lists of relevant articles were hand searched, as well as citing articles. References were uploaded to EndNote (Clarivate Analytics, Philadelphia, PA) and screened for relevance.

Selection Criteria

Only studies with the primary objective of examining symptom improvement with a specific intervention (e.g., treatment with vestibular rehabilitation) in VM patients were included. Relevant outcome measures are described below. Abstracts were first independently reviewed by two reviewers (Y.J.B. and D.A.L.) to first identify all articles pertaining to the treatment of vestibular migraine or its equivalent. Non-English studies, nonhuman studies, and nonjournal articles were excluded. Case reports and review articles were first included for the screening of their content and references but were excluded from the final analyses.

Studies were considered for inclusion in the final analysis if they were 1) double- or single-blinded randomized controlled trials, 2) double- or single-blinded randomized comparison trials, or 3) prospective or retrospective observational studies or case series that measured symptom outcome after treatment of vestibular migraine. We anticipated a small number of studies where the participants fulfill the 2012 Bárány Society/IHS criteria[5] for vestibular migraine. To increase the number of studies in the final set, studies that used previous 2001 Neuhauser et al. criteria[4] were also included. Studies that included patients with migraine in addition to vestibular symptoms were also screened and determined for inclusion and further analysis.

Outcome measures that are relevant to the health care providers and general public were extracted by two reviewers (Y.J.B. and D.A.L.) and included in the analysis and discussion. Disagreements were resolved in a discussion with a third reviewer (S.A.N.). Primary outcome measures included quality-of-life measures, the intensity of vestibular symptoms, the number of symptom episodes, and the overall perceived improvement in symptoms. However, outcomes that were reported with statistics that could not be used were excluded. In instances of incomplete data, two attempts were made to contact the primary author via email for clarification or sharing of primary data. Level of evidence for each selected article was evaluated with the Oxford Center for Evidence-Based Medicine.[17] The risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.[18] Two authors (Y.J.B. and D.A.L.) performed a pilot assessment on three studies to check for consistency of assessment. Both then performed independent risk assessment on the remaining studies. All disagreements were resolved by the way of discussion with a third author (S.A.N.). Risk of bias items included the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and

other bias. The risk of bias for each aspect is graded as low, unclear, or high.

Statistical Analysis

Meta-analysis of included studies utilized preintervention (baseline) to postintervention measures, with all subjects serving as their own controls. For the purpose of comparison, investigated treatments for vestibular migraine were grouped according to their class: antiepileptic drug (AED), calcium channel blocker (CCB), β-blocker (BB), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic acid (TCA), ergot, vestibular rehabilitation, or diet. Analyses of continuous measures (means and standard deviations between pre- and postintervention) were performed with Cochrane Review Manager (RevMan) version 3.5 (Nordic Cochrane Centre, Cochrane Collaboration, 2011, Copenhagen, Denmark). The null hypothesis in this study was that there was no difference between before and after intervention with respect to Dizziness Handicap Index (DHI), vertigo frequency (VF), or the intensity of vertigo attacks. In addition, we aimed to determine if the type of therapy had any effect on the percentage of patients who received symptomatic improvement (defined as >50% reduction in subjective symptoms). Data are presented as mean ± standard deviation (SD) with 95% confidence interval (CI) in the text and as mean difference (MD) in the figures. Wherever appropriate, MD was calculated from baseline measurements to short-term follow-up measurements (≤12 weeks), baseline to long-term measurements (>12 weeks), and between short- and long-term measurements. The total MD with 95% CI is given for both the fixed- and random-effects models. Under the fixed-effects model, it is assumed that all studies come from a common population, and that the effect size as measured through MD is not significantly different among the different trials. This assumption is tested by the heterogeneity test or I^2 statistic. If this test yields a low probability value ($P < .05$), then there is a high likelihood the fixed-effects model is invalid and the random-effects model is more appropriate. The random-effects model incorporates both the random variation within the studies and the variation between the different studies.[19] The random-effects model provides a more conservative estimate (i.e., a wider CI), but the results from the two models typically agree when there is no heterogeneity. When heterogeneity was present, the random-effects model was the preferred model. In addition, a meta-analysis of proportions was performed using MedCalc 19.0.4 (MedCalc Software, Ostend, Belgium). The MedCalc program lists the proportions (expressed as a percentage) with their 95% CIs, found in the individual studies included in the meta-analysis. MedCalc used a Freeman-Tukey transformation[20] to calculate the weighted summary proportion under the fixed- and random-effects model. Heterogeneity testing was performed as previously described. Each study was weighted according to the number of patients included. Both the fixed-effects model and the random-effects model were used in this study. For categorical data, meta-analysis of proportions was performed using MedCalc 19.0.4.

RESULTS

Included Studies

A total of 13 different publications were included in the meta-analysis.[14,21–32] A PRISMA diagram outlining the literature search is shown in Figure 1. Oxford level of evidence was assessed for included studies and can be seen in Table II. These studies were published from 2002 to 2017 and originated from 12 different countries. There were 23 separate treatment arms of monotherapeutic interventions. Although diet is listed as an individual intervention in several studies (n = 3), multiple treatment protocols reported herein report outcomes for pharmacologic treatment among individuals who were also advised for dietary restriction. Other treatment arms were AED (three), CCB (six), TCA (three), BB (two), SNRI (three), vestibular rehabilitation (two), and ergot (one). Assessment of risk of bias is shown in Figure 2.

Outcomes were reported on 468 individual patients with mean age of 43.3 years (range, 8–84 years). Reported gender was 113 males and 323 females (specific gender for each treatment arm was not routinely available for all studies), with female-to-male ratio of 2.1:1. This group comprised 264 individuals from six studies[25,27–31] with either probable or definitive VM according to the Bárány/IHS criteria, 160 individuals from six studies[21–24,26,32] with VM according to Neuhauser criteria, and 44 individuals from one study[14] with migraine with vertigo symptoms as determined by the author. Although different diagnostic criteria are used among these studies, the represented population may not be heterogeneous, and those fulfilling Neuhauser criteria may represent at least probable VM according to the Bárány/HIS criteria.

Summary of Findings

Three different measurable outcomes were evaluated in the present study: DHI, VF, and percentage of patients that achieved ≥50% symptom resolution. Other outcomes such as headache and vertigo attack intensity were insufficiently reported in the available studies to be included in the meta-analysis.

Dizziness Handicap Inventory

Four studies containing seven individual treatment arms reported baseline DHI for 177 patients (Fig. 3). Short-term responses were reported for all treatment arms, whereas long-term measurements were only reported in two of the arms. The range of follow-up for short-term responses was 4–12 weeks, with the range of long-term responses being 16–24 weeks. Treatment arms with available DHI data were vestibular rehabilitation (two), SNRI (two), BB (one), AED (one), and CCB (one). All treatment arms reported reductions in DHI. The overall MD in short-term effect was −15.92 (95% CI: −23.25 to −8.33). The largest short-term MD was reported in the BB group (−24.5, 95% CI: −33.48 to −15.52), and the smallest MD was seen in the CCB group (−6.82, 95% CI: −16.52 to 2.88). With vestibular rehabilitation, the MD from baseline to long term was −20.98 (95% CI: −29.11 to −12.85), and the MD between short and long term was −5.90 (95% CI: −14.53 to 2.73).

Vertigo Frequency

Six studies encompassing nine treatment arms reported changes in mean frequency of monthly vertigo attacks with various interventions (Fig. 4). Treatments

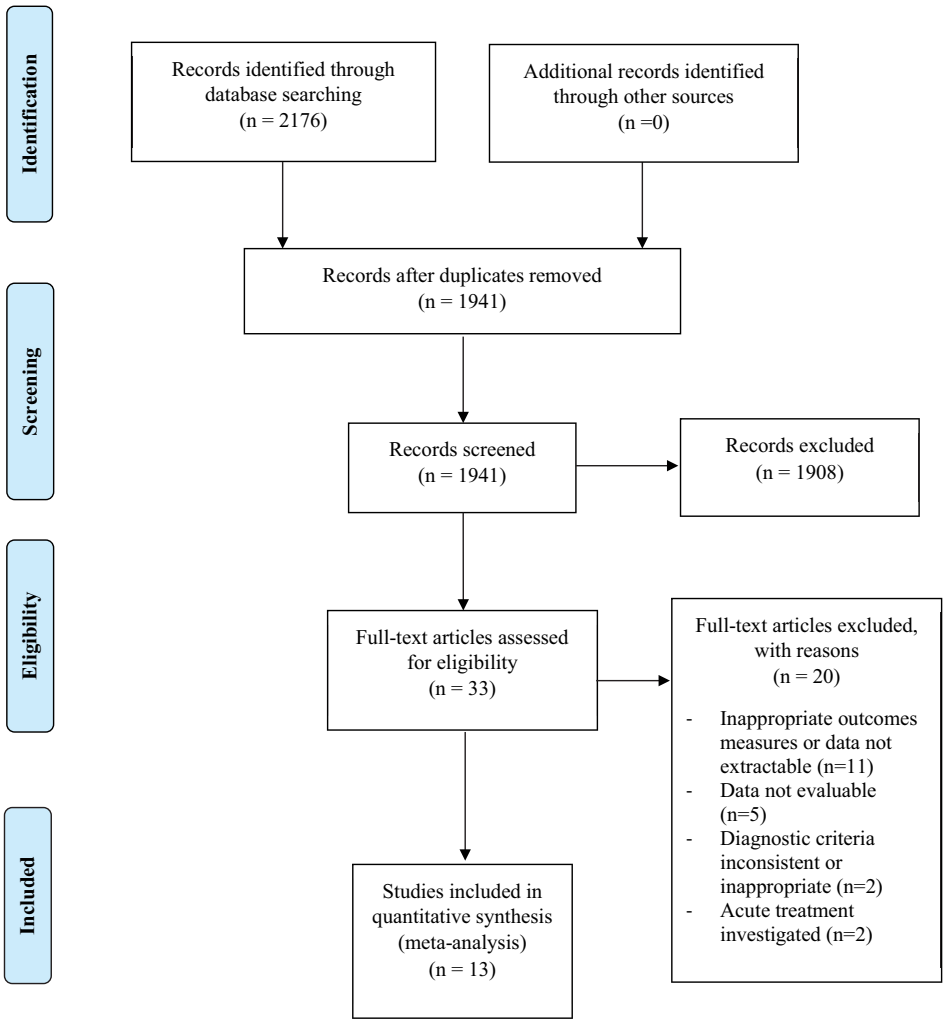

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

were CCB (three studies, n = 68), AED (two studies, n = 39), SNRI (two studies, n = 54), BB (1 study, n = 33) and vestibular rehabilitation (1 study, n = 28). Short-term effects were reported in seven studies, with an overall MD of −3.59 (95% CI: −5.01 to −2.17). The largest MD was in the 26 individuals who received BB (−10.70, 95% CI: −14.49 to −6.91), whereas the smallest MD was reported among the 28 subjects in the rehabilitation group (−1.93, 95% CI: −3.15 to −0.71). Overall MD for long-term follow-up from baseline was −2.89 (95% CI: −5.56 to −0.22). One study reported interval change from short- to long-term change for VF (rehabilitation, n = 28; MD = −0.47, 95% CI: −1.67 to 0.73).

Symptom Improvement

Seven additional studies reported proportion of patients who experienced >50% improvement in their symptomatology (Table III). A total of 248 patients comprised 14 treatment arms in seven different intervention groups: CCB (four studies, n = 100), TCA (three studies, n = 50), diet modification (three studies, n = 49), AED (n = 16), BB (n = 30), SNRI (n =1), and ergot (n = 2). The overall proportion of patients who experienced improvement was 69.6% (95% CI: 53.84 to 83.30). The meta-analysis of proportions for each treatment group showed improvement in 68.25% (95% CI: 54.02 to 80.35) of patients on TCA, 75.53% (95% CI: 8.51 to 94.36) for diet modification, and 76.67% (95% CI: 67.36 to 84.40) for CCB. AED and BB were each assessed in one study, and 25.00% and 73.33% of the patients showed improvement, respectively.

Side Effects

Tolerability and adverse events were mentioned in nine publications.[14,21,22,24–27,29,30] One investigation studying lamotrigine[21] reported no adverse events were experienced, whereas two studies[14,26] examining nortriptyline and topiramate nonspecifically stated that some patients were unable to tolerate the medications, resulting in six out of 47 patients from the nortriptyline group (13%) and four out of 17 from the topiramate group

TABLE II.
Descriptive Features of Included Studies in the Final Analysis.

Article	Country	OLE	No.	Treatment Arm (Label)	Class	Mean Age ± SD (Range)	Male	Female	Outcome
Bisdorff 2004	Luxemburg	4	19	Lamotrigine	AED	52.3 ± 20.2 (28–84)	6	13	HA, VF
Iwasaki 2007	Japan	4	22	Lomerizine (a)	CCB	40.0 (18–62)*	23*	10*	50% improvement
			4	Diet alone (b)	Diet	*	*	*	50% improvement
			2	Dihydroergotamine (c)	Ergot	*	*	*	50% improvement
			1	Paroxetine (d)	SNRI	*	*	*	50% improvement
Jay-du Preez 2011†	South Africa	4	2	Amitriptyline	TCA	34 (14–50)	0	2	50% improvement
Lepcha 2014	India	2b	25	Flunarizine	CCB	32.0	10	16	50% improvement
Liu 2017	China	2b	23	Venlafaxine (a)	SNRI	53.2 ± 15.6	7	16	DHI, VF
			22	Flunarizine (b)	CCB	51.5 ± 15.4	8	14	DHI, VF
			20	Valproic acid (c)	AED	52.4 ± 16.0	5	15	DHI, VF
Mikulec 2012	USA	4	32	Diet/caffeine (a)	Diet	44.0 (22–68)	9	32	50% improvement
			16	Nortriptyline (b)	TCA	*	*	*	50% improvement
			17	Topiramate (c)	AED	*	*	*	50% improvement
Reploeg 2002†	USA	4	13	Diet (a)	Diet	*	*	*	50% improvement
			31	Nortriptyline (b)	TCA	36.6 (8–71)*	8*	23*	50% improvement
Salviz 2016	Turkey	2b	33	Propranolol (a)	BB	38.0 (18–60)	2	31	DHI, VF
			31	Venlafaxine (b)	SNRI	42.0 (21–60)	3	28	DHI, VF
Sugaya 2017	Japan	4	28	Rehab	Rehab	47.7 ± 18.2	0	28	DHI, HA, VF
Taghdiri 2014	Iran	4	24	Cinnarizine	CCB	31.2 ± 8.0 (18–54)	1	23	HA, VF
Teggi 2015	Italy	4	22	Cinnarizine	CCB	41.8 ± 7.7	5	17	HA, VF
Van Ombergen 2015	Belgium	4	30	Propranolol (a)	BB	46.5	10	20	50% improvement
			31	Flunarizine (b)	CCB	46.5	10	21	50% improvement
Vitkovic 2013	Australia	4	20	Rehab	Rehab	46.8 (28–70)	6	14	DHI

*Specific demographics from individual treatment arms not reported.
†Presents additional data on patients treated with combination therapy; these patients were excluded from analysis.
AED = antiepileptic drug; BB = β-blocker; CCB = calcium channel blocker; DHI = Dizziness Handicap Index; HA = headache frequency; OLE = Oxford level of evidence; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; VF = vertigo attack frequency.

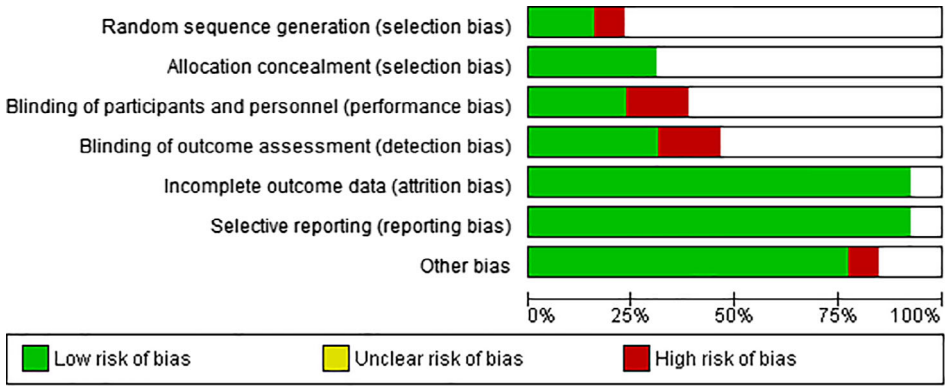

Fig. 2. Assessment of risk of bias. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

(24%) discontinuing therapy. Side effects reported for venlafaxine[25,27] included nausea, insomnia, palpitation, lethargy or fatigue, somnolence, and sexual dysfunction; overall, eight patients out of 54 (15%) discontinued treatment with venlafaxine due to adverse effects. Propranolol was associated with bronchospasm, hypotension, or syncope, resulting in four patients out of 63 (6%) discontinuing treatment.[27] Reported side effects for CCBs were weight gain, somnolence, and gastrointestinal upset.[22,24,25,29,30] One patient out of 22 (5%) in the lomerizine group discontinued treatment due to adverse effect (fatigue).[22] Investigation with valproic acid reported nausea, somnolence, and indigestion, resulting in two patients dropping out due to these effects[25] out of 20 patients (10%). Due to inconsistencies in reporting and possible clinical redundancy, further analysis on these adverse events was not performed.

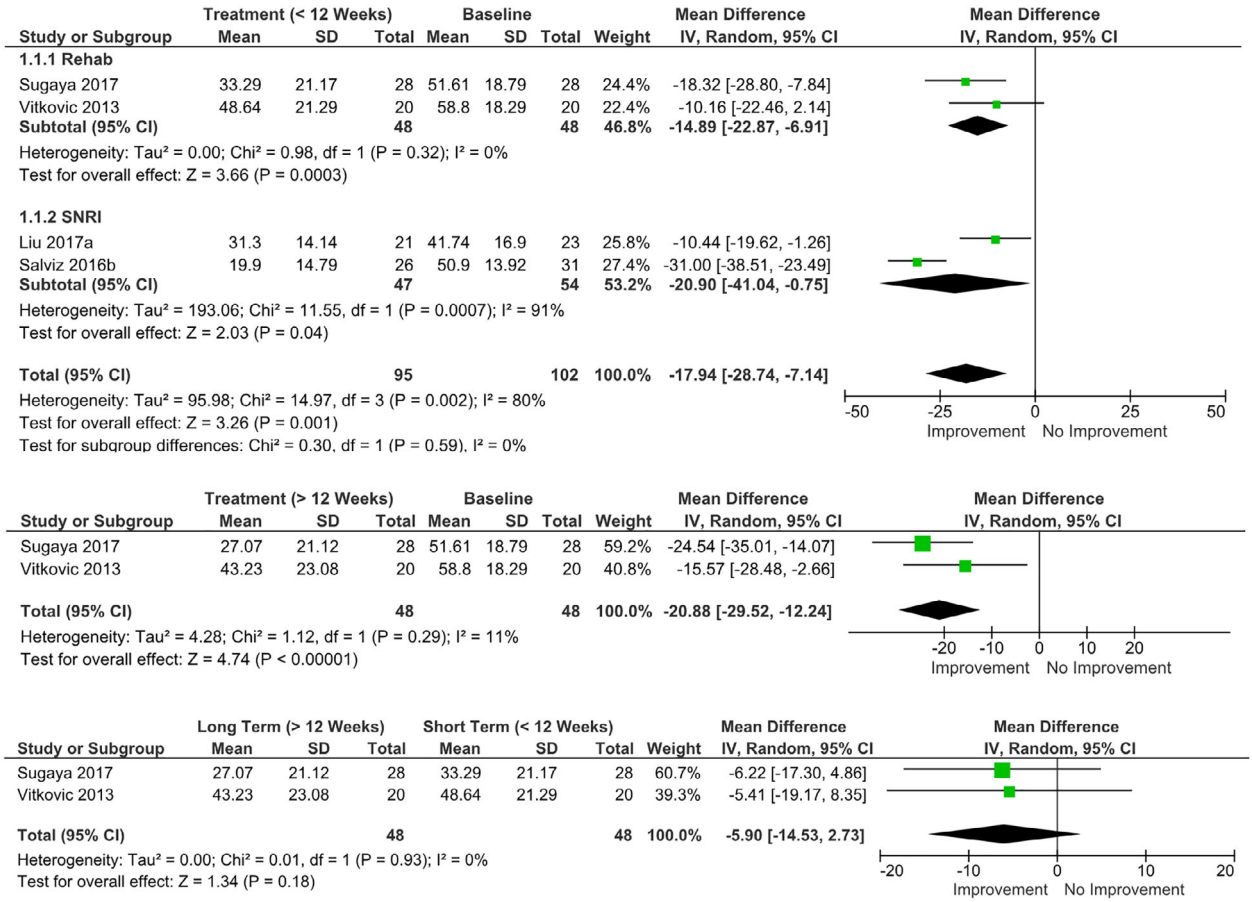

Fig. 3. Forest plot of mean difference (MD) on the Dizziness Handicap Inventory (DHI) from baseline to short-term and long-term follow-up. Meta-analysis of DHI. The top panel shows the MD in DHI from baseline to short-term follow-up (<12 weeks). The middle panel shows the MD from baseline to long-term follow-up (>12 weeks). The bottom panel shows the MD from short-term to long-term follow-up. Letters a or b after study name represent separate treatment arms within the same study. CI = confidence interval; IV = inverse variance; Rehab = vestibular rehabilitation; SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

DISCUSSION

The purpose of this meta-analysis was to assess the available data on the efficacy of various pharmacologic and nonpharmacologic interventions for the prevention of VM. Consistent with the findings from prior investigations,[8,10] our demographic results show female preponderance with an average age of approximately 43 years old. Various classes of therapeutic agents were assessed for VM prophylaxis, including AEDs, CCBs, TCAs, BBs, SNRIs, and vestibular rehabilitation. All treatment options demonstrated improvement in DHI and VF, but due to significant heterogeneity and lack of standardized reporting on outcomes, establishment of preferred treatment modality could not be determined.

Unfortunately, other factors associated with VM, such as anxiety and depression,[1] were not able to be analyzed in this study. The only patient-reported outcome measure included in this meta-analysis was the DHI, which is a symptom-specific questionnaire (and not etiology specific) and does not always capture the extent of the impact of VM on patients. This measure is a patient-reported assessment designed to evaluate patient's functional, emotional, and physical limitations due to perceived dizziness.[33] The largest improvement in DHI was seen with BB use (propranolol), followed by SNRI (venlafaxine) use in the short-term follow-up; similar improvement was seen with vestibular rehabilitation in the long-term follow-up. Statistical comparison between drug classes was not performed due to limited statistical power. Some authors advocate venlafaxine as first-line therapy for VM for its strong association with psychiatric comorbidities.[25,27,34,35] Interestingly, Salviz et al. noted that depressive symptoms alleviated only with venlafaxine when compared to propranolol.[27] Furthermore, venlafaxine also showed better improvement on the emotional scale on DHI.[25,27] These pharmacological agents were effective in ameliorating the frequency of vertigo attacks as well; overall MD in VF for propranolol and venlafaxine were 10.7 and 5.9, respectively.

Vestibular rehabilitation is often used as a nonmedical treatment option for those with vestibular symptoms, and its efficacy has been demonstrated previously.[36,37] Some authors have suggested avoiding vestibular suppressants with vestibular rehabilitation due to the concern that they may influence the rate of central compensation.[38,39]

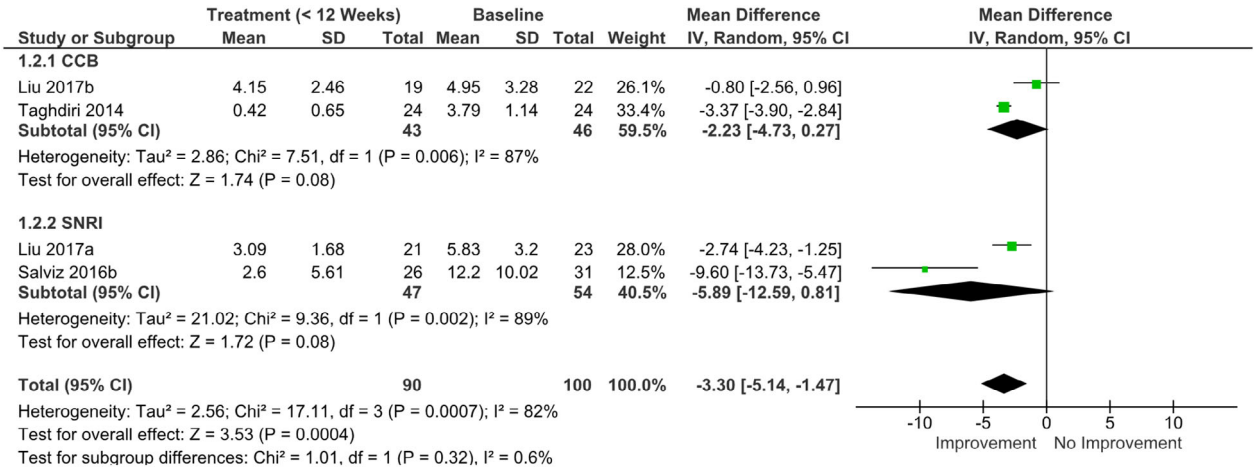

Fig. 4. Forest plot of mean difference (MD) on frequency of vertigo attacks per month (VF) from baseline to short-term follow-up. Meta-analysis of VF. Panel shows the MD in VF from baseline to short-term follow-up (<12 weeks). CCB = calcium channel blocker; CI = confidence interval; IV = inverse variance; SD = standard deviation; SNRI = serotonin-norepinephrine reuptake inhibitor. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

TABLE III.
List of Various Therapies Associated With Patients Reporting >50% Symptom Improvement.

Article	Drug	No.	N of Patients With >50% Improvement*	Mean Follow-up, wk
AED				
Mikulec 2012c	Topiramate	16	4	NR
BB				
Van Ombergen 2015a	Propranolol	30	22	NR
CCB				
Iwasaki 2007a	Lomerizine	22	19	4.0–8.0
Teggi 2015	Cinnarizine	22	15	24
Lepcha 2014	Flunarizine	25	22	12
Van Ombergen 2015b	Flunarizine	31	21	NR
Diet				
Iwasaki 2007b	Diet alone	4	4	4.0–8.0
Mikulec 2012a	Caffeine cessation	32	5	NR
Reploeg 2002a	Diet alone	13	13	54.5
SNRI				
Iwasaki 2007d	Paroxetine	1	1	4.0–8.0
TCA				
Reploeg 2002b	Nortriptyline	31	24	54.5
Mikulec 2012b	Nortriptyline	17	8	NR
Jay-du Preez 2011	Amitriptyline	2	2	NR
Other				
Iwasaki 2007c	Dihydroergotamine	2	1	4.0–8.0

*In cases where improvement of both headache frequency and vertigo were reported, this table represents improvement in vertigo.
Letters a, b, or c after study name represent separate treatment arms within the same study.
AED = antiepileptic drug; BB = β-blocker; CCB = calcium channel blocker; NR = not reported; SNRI = serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

However, Vitkovic et al. demonstrated that no significant effect of medication use was observed on the physical performance score.[32] Whitney et al., though not included in this analysis due to lack of SDs associated with results, showed that rehabilitation alone improved the DHI score, and medicine use further potentiated improvement.[36] Interestingly, statistically significant improvements were demonstrated on the physical and functional subscale of DHI but not on the emotional subscale. That is, although the patients demonstrated improvement in their physical

performance, they still felt emotionally handicapped, possibly due to persistent severity of vestibular symptoms. Stratification of the DHI subscale was not provided in the studies included in our analysis, precluding our ability to assess the effect of rehabilitation on the emotional scale. Overall, vestibular rehabilitation demonstrated improvement of symptoms in all parameters. Although no superiority over pharmacologic agent was demonstrated, the efficacy of the rehabilitation was seemingly more pronounced with longer follow-up period.

CCBs are a class of drug that have long been utilized in the treatment of VM. In the present study, we reported on data from 46 subjects who had received various CCBs, including flunarizine, cinnarizine, and lomerizine. Although these medications are not currently available in the United States, they consistently appear as one of the therapeutic options for VM internationally. Verapamil and amlodipine are CCBs that are available in the United States; however, investigations regarding its use in VM are lacking. The proposed rationale for using this class of drugs is based upon previous literature in which a genetic deficiency in voltage-gated calcium channels was identified in patients with familial hemiplegic migraine and type II episodic ataxia; these paroxysmal disorders are characterized by vertigo and migraine as the major symptoms.[40] Although it was hypothesized that a genetic defect in the same region would be associated with VM, there was no evidence suggesting these genes increase susceptibility for VM.[41,42] The present meta-analysis of CCBs showed improvement of symptoms in all parameters in our analysis, including DHI and VF. However, superiority over other drugs could not be demonstrated due to limited data and poor power. Overall, CBBs were effective in reducing symptoms in 76.67% of patients.

AEDs represent an additional pharmacological class used for the prophylactic treatment of migraine.[43–45] They act through various mechanisms of action that ultimately modulate neural systems involved in the pathophysiology of migraine.[44] Their effectiveness in VM is demonstrated in our study, where valproic acid showed reduction in DHI and VF, and lamotrigine in VF. However, AED use is often hindered by side effects that require treatment discontinuation. In present study, two out of 20 patients and four out of 15 patients dropped out due to adverse events associated with valproic acid and topiramate use, respectively. The side effect of topiramate was not clearly described in the included study. In an investigation by Gode et al., not included in our analysis due to nonevaluable data, reductions in frequency and intensity of headache and vertigo attacks were observed with topiramate use after 24 weeks.[46] However, its use was limited by side effects: paresthesia (19/30), fatigue (11/30), memory/concentration issues (8/30), decreased appetite (14/30), and weight loss (4/30). Four patients discontinued treatment in this study due to adverse effects.

The therapeutic response to episodic disorders such as VM is difficult to study due to natural fluctuation in disease symptoms. For instance, improvement in symptoms after 1 month may be due to a natural spontaneous remission rather than a response to a therapeutic intervention. Hence, a longer follow-up period may confer better reliability of therapeutic response. This should be considered with the fact that longer duration of follow-up could lead to lower patient compliance to treatment due to adverse effects. Included in our analysis were nine studies that reported adverse effects associated with the interventions; patient dropout due to adverse effects was noted in treatments with valproic acid, propranolol, venlafaxine, lomerizine, nortriptyline, and topiramate. The most common follow-up length was 12 weeks, which allowed adequate time for medications to take effect. In the included studies, most patients who discontinued treatment did so within 1 month of intervention initiation, suggesting that adverse events from these treatments occur early in therapeutic management.

Although comprehensive in nature, this study has several limitations. Given that the diagnostic criteria for VM were codified as recently as 2012 by the Bárány Society and IHS, we expected few studies to adopt these specific diagnostic criteria. Furthermore, Formeister et al.[1] highlight the issue of widespread underdiagnosis of the condition. In an attempt to expand the number of studies and capture a broader range of patients who may fulfill the 2012 diagnostic criteria, we included studies between 2000 and 2012 that included patients with migraine and vestibular symptoms. However, this attempt may have resulted in a more heterogeneous population with imprecise disease status. Because this is a meta-analysis of only published data, lack of individual patient data precluded accurate characterization of disease status.

Another limitation inherent to the present study design was the inability to include trials with polypharmacologic treatment arms. Several studies in our initial literature search employed dual or triple therapies to achieve optimal symptom management, making analysis of individual treatment modality difficult. Ultimately, these studies were excluded from the present analysis in an effort to specifically explore the effects of monotherapy in this population. One retrospective investigation of BBs, AEDs, TCAs, and CCBs by Baier et al. observed decreases in frequency, duration, and intensity of vertigo attacks.[47] A second observational study among children with VM reported that many subjects required more than one prophylactic treatment to achieve optimal disease control without clearly delineating which treatment combinations were used for each patient.[48] Finally, a prospective observational study by Lee et al. permitted physician selection of BB, CCB, TCA, and/or AED for VM prophylaxis, reporting that all parameters of vertigo, headache, and quality of life improved without stratifying outcomes by therapeutic selection.[11]

To date, there are no completed double-blinded, randomized controlled trials for the treatment of VM. Most of the available data are drawn from trials that were uncontrolled clinical observational or comparison studies with a retrospective design; hence, there are no robust trials with high levels of evidence from which to extract data, and the included studies are subject to reporting biases. Furthermore, the variabilities in the treatment modalities, dosages, and subjective outcome measures limit the generalizability of the results.

Although lack of rigorous trials compromises the level of evidence and the strength of recommendation, it

draws attention to the current status on VM treatment and the need for new investigations to answer these questions. Future randomized controlled trials with restrictive inclusion criteria will make prospective meta-analyses more methodologically robust. We endorse and encourage the use of the 2012 Bárány Society/IHS criteria for vestibular migraine in future studies to standardize the diagnostic criteria and reduce clinical heterogeneity.

CONCLUSION

Various treatment modalities have been evaluated for preventative treatment of VM. Due to significant heterogeneity and lack of standardized reporting on outcomes, establishment of preferred treatment modality could not be determined. The side-effect profiles of various pharmacologic agents as well as patient comorbidities likely influence the selection of intervention. The effectiveness of treatment should be evaluated after adequate duration of intervention.

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