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Network Meta-analysis of Different Treatments for Vestibular Migraine

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Abstract

Introduction Although one of the major presentations of vestibular migraine is dizziness with/without unsteady gait, it is still classified as one of the migraine categories. However, in contrast to ordinary migraine, vestibular migraine patients have distinct characteristics, and the detailed treatment strategy for vestibular migraine is different and more challenging than ordinary migraine treatment. Currently, there is no conclusive evidence regarding its management, including vestibular migraine prophylaxis.

Aim The objective of this current network meta-analysis (NMA) was to compare the efficacy and acceptability of individual treatment strategies in patients with vestibular migraine.

Methods The PubMed, Embase, ScienceDirect, ProQuest, Web of Science, ClinicalKey, Cochrane Central, and ClinicalTrials.gov databases were systematically searched for randomized controlled trials (RCTs), with a final literature search date of 30 December 2022. Patients diagnosed with vestibular migraine were included. The PICO of the current study included (1) patients with vestibular migraine; (2) intervention: any active pharmacologic or non-pharmacologic intervention; (3) comparator: placebo-control, active control, or waiting list; and (4) outcome: changes in migraine frequency or severity. This NMA of RCTs of vestibular migraine treatment was conducted using a frequentist model. We arranged inconsistency and similarity tests to re-examine the assumption of NMA, and also conducted a subgroup analysis focusing on RCTs of pharmacological treatment for vestibular migraine management. The primary outcome was changes in the frequency of vestibular migraines, while the secondary outcomes were changes in vestibular migraine severity and acceptability. Acceptability was set as the dropout rate, which was defined as the participant leaving the study before the end of the trial for any reason. Two authors independently evaluated the risk of bias for each domain using the Cochrane risk-of-bias tool.

Results Seven randomized controlled trials ($N = 828$, mean age 37.6 years, 78.4% female) and seven active regimens were included. We determined that only valproic acid (standardized mean difference [SMD] −1.61, 95% confidence interval [CI] −2.69, −0.54), propranolol (SMD −1.36, 95% CI −2.55, −0.17), and venlafaxine (SMD −1.25, 95% CI −2.32, −0.18) were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups. Furthermore, among all the investigated pharmacologic/non-pharmacologic treatments, valproic acid yielded the greatest decrease in vestibular migraine frequency among all the interventions. In addition, most pharmacologic/non-pharmacologic treatments were associated with similar acceptability (i.e. dropout rate) as those of the placebo/control groups.

Conclusions The current study provides evidence that only valproic acid, propranolol, and venlafaxine might be associated with beneficial efficacy in vestibular migraine treatment.

Trial registration CRD42023388343.

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1 Introduction

Despite the symptomatology of dizziness during a migraine attack, vestibular migraine is considered a distinct subtype of migraine [1–3]. Vestibular symptoms can occur in the absence of headache or migraine episodes in patients with vestibular migraine. Unlike ordinary migraine, vestibular migraine has distinct characteristics [4]. Specifically, patients with vestibular migraine had a significantly higher balance

Key Points

Vestibular migraines have long been ignored and misdiagnosed. In contrast to ordinary migraine, vestibular migraine patients have distinct characteristics, and the detailed treatment strategy for vestibular migraine is different and more challenging than ordinary migraine treatment. Currently, there is no conclusive evidence regarding its management, including vestibular migraine prophylaxis.

This network meta-analysis of seven randomized controlled trials (RCTs) of vestibular migraine treatment demonstrated that only valproic acid, propranolol, and venlafaxine were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups. Furthermore, among all the investigated pharmacologic/non-pharmacologic treatments, valproic acid yielded the most decreased vestibular migraine frequency among all the interventions. In addition, most pharmacologic/non-pharmacologic treatments were associated with acceptability and safety profiles similar to those of the placebo/control groups.

The current study provides evidence that only valproic acid, propranolol, and venlafaxine might be associated with beneficial efficacy in vestibular migraine treatment.

disability but fewer headache symptoms than patients with migraine. Furthermore, vestibular migraine patients are more likely to be depressed than normal migraine patients [4]. The management strategy for vestibular migraine is similar to that for ordinary migraine. Specifically, the management strategy for vestibular migraine would emphasize acute treatment to an acute attack and prophylactic treatment to prevent the next episode. However, the detailed treatment strategy for vestibular migraine is different and more challenging than ordinary migraine treatment [5, 6].

Several large-scale network meta-analyses (NMAs) of pharmacologic [7, 8] or non-pharmacologic [9] treatments have focused on ordinary migraine prophylaxis; however, unlike ordinary migraines, there have been few studies on vestibular migraine prophylaxis. Most of these studies had low evidence levels, such as retrospective reports or non-RCTs [5]. Sharing the overlapping pathophysiology with ordinary migraine, some effective medications in ordinary migraine prophylaxis, such as valproic acid, also provide

efficacy in vestibular migraine prophylaxis [10]. However, not all medications that are effective for ordinary migraine have significant efficacy for vestibular migraine. For example, a recent RCT failed to show the efficacy of metoprolol in vestibular management [11]. Among the currently available trials, most did not clearly distinguish participants with vestibular migraine from those with ordinary migraine. Therefore, these methodological limitations would restrict our interpretation and application of these results in clinical practice for patients with vestibular migraine [5].

The NMA has the advantage of allowing for multiple comparisons of efficacy between individual treatment strategies for vestibular migraine prophylaxis. Such evidence from an NMA can inform clinical practice [12]. The aim of our NMA was to compare the efficacy and acceptability of individual treatment strategies in patients with vestibular migraine. In addition, to provide evidence that is more specific to vestibular migraine, we only included RCTs of definite vestibular migraine, which were diagnosed according to specific well-defined diagnostic guidelines [1–3].

2 Methods

2.1 General Description for the Current Study

The current NMA complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13] and AMSTAR 2 guidelines [14]. After approval by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No. B-109-29), we registered this study in the PROSPERO database (registration: CRD42023388343).

2.2 Searches

We retrieved eligible RCTs from the PubMed, Embase, ScienceDirect, ProQuest, Web of Science, ClinicalKey, Cochrane CENTRAL, and ClinicalTrials.gov databases (electronic supplementary material [ESM] Table 1); the gray literature was searched in ClinicalTrials.gov. The final date of the literature search was 30 December 2022. No language restrictions were applied. We also arranged a manual search to find articles cited in review articles and pairwise meta-analyses [15–18].

2.3 Inclusion/Exclusion Criteria

The PICO of the current study included (1) patients with vestibular migraine; (2) intervention: any active pharmacologic or non-pharmacologic intervention; (3) comparator:

placebo-control, active control, or waiting list; and (4) outcome: changes in migraine frequency or severity. We only included RCTs that reported on vestibular migraine patients for efficacy of pharmacological or non-pharmacological interventions for vestibular migraine management. The inclusion criteria were (1) RCTs; (2) human participants; and (3) patients with a diagnosis of vestibular migraine. A diagnosis of vestibular migraine can be established according to well-defined diagnostic guidelines [1–3]. Exclusion criteria were (1) not clinical trials; (2) not RCTs; (3) did not include target outcomes of interest; or (4) not specific to patients with vestibular migraine. In situations where the same set of data had been used by multiple studies, we used the study with the most information or with the largest sample size.

2.4 Data Extraction

The eligible studies were screened by two authors to determine their inclusion/exclusion. Data of interest were extracted from the included studies, and the risk of bias was assessed by the aforementioned two authors. Where these authors disagreed, the corresponding author adjudicated the disagreements. If the manuscript lacked relevant data, we contacted the corresponding authors or co-authors to obtain the data of interest. We followed the research process of our previous NMAs on migraine management [7–9, 19–21].

2.5 Variables and Outcomes

Because the goal of treatment for vestibular migraine is not complete remission but a reduction in vestibular migraine frequency [22, 23], we selected the changes in vestibular migraine frequency to be the primary outcome. With regard to data extraction of the outcome 'changes in migraine frequency', because not all vestibular migraineur patients were able to clearly recognize the current episode to be a vestibular migraine attack, other type of headache, or other type of vertigo, the RCTs applying migraine diaries might have some methodological limitations. Therefore, if there was 'changes in migraine frequency', 'changes in headache frequency', and 'changes in vertigo frequency' in one RCT, we selected 'changes in migraine frequency' first. If there were no 'changes in migraine frequency', we chose to use 'changes in headache frequency' or 'changes in vertigo frequency'. The secondary outcomes were changes in the vestibular migraine severity, acceptability, and safety profiles. Acceptability was calculated using the dropout rate, i.e., the proportion of patients leaving the study before the end of the trial due to any reason. The safety profile was set as any adverse effect rate, which was defined as a participant

encountering any adverse effect during the study regardless of whether the treatment was related or not.

2.6 Cochrane Risk-of-Bias Tool

The risk of bias (interrater reliability = 0.85) was assessed by two authors using the Cochrane risk-of-bias tool [24].

2.7 Statistical Analysis

We performed NMA using STATA version 16.0 (StataCorp LLC, College Station, TX, USA). The standardized mean difference (SMD) and odds ratio (OR), accompanied with their corresponding 95% confidence intervals (CIs), were calculated for continuous and categorical data, respectively. With regard to OR, we applied a 0.5 zero-cell correction in the meta-analysis procedure; however, for studies with 0 in both the intervention and control arms, we did not apply such a correction because bias might be increased by doing so [25, 26]. The current NMA was based on the frequentist model. A two-tailed test, with a p value <0.05 indicating statistical significance, was used to compare the effect size. Heterogeneity was evaluated using the tau statistic.

We arranged a mixed comparison with a generalized linear mixed model to analyze the direct/indirect comparisons in this NMA [27]. The indirect comparisons were conducted by the assumption of transitivity; in other words, we assumed that the hitherto unknown difference between treatments A and B could be determined from the known differences between A and C and between B and C, where C is the third treatment. Furthermore, to make multi-arm comparisons, we combined direct/indirect evidences from the recruited studies [28]. We used the *mvmeta* command in STATA [29]. The restricted maximum likelihood method was applied to investigate the between-study variance [30]. To increase the clinical applicability of our findings, we calculated the surface under the cumulative ranking curve (SUCRA) to rank the probability of relative superiority of individual treatments compared with others [31]. Although the concept of probability was mainly based on the Bayesian model, the module of White (2015) could simulate the probability and deal with a multi-arm trial according to the calculated data from the frequentist model so that we could achieve the SUCRA conclusion [32].

Finally, to support the assumptions of similarity/transitivity/consistency, we arranged the following analyses. First, in line with the rationale of our previous NMA studies [9, 33], this study assessed the effectiveness of the different control interventions (i.e., changes in vestibular

migraine frequency by either controls or placebo) to justify our assumption of similarity. Specifically, this study computed the changes in vestibular migraine frequency in the 'RCT with placebo' group and 'RCT with controls' group using Comprehensive Meta-Analysis (version 3; Biostat, Englewood, NJ, USA) [34]. Later, we evaluated transitivity/consistency using a loop-specific approach, node-splitting method, and design-by-treatment model [35].

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tools were chosen to evaluate the quality of overall evidence following the rationale of previous studies conducted by Puhan et al. [36] and Cipriani et al. [37]. Finally, to reduce the potential source of heterogeneity, we conducted a subgroup analysis focusing on RCTs of pharmacological treatment for vestibular migraine management.

3 Results

After the initial screening procedure, 23 articles were considered for full-text review (Fig. 1). Overall, 16 articles were excluded for various reasons (Fig. 1 and ESM Table 2) [15–18, 38–49], leaving seven articles for final inclusion in the NMA (Table 1) [11, 50–55]. The overall network structure of the treatment arms is shown in Fig. 2.

3.1 Characteristics

These seven RCTs, published between 2014 and 2022, included 828 participants in total. The mean age was 37.6 years (range 32.5–52.4 years) and 78.4% of participants were female (range 60.8–92.2%). The mean study duration was 14.9 weeks (range 12–24 weeks). None of the RCTs prohibited the concurrent use of anti-migraine medication. The vestibular migraine diagnosis was made according to Neuhauser et al. [1], Lempert et al. [2], or the International Classification of Headache Disorders 3rd edition criteria [3]. The investigated treatment arms included seven active regimens (flunarizine, propranolol, venlafaxine, metoprolol, valproic acid, resistance exercise, and probiotic L. casei Shirota) and one control arm (placebo or treatment as usual).

3.2 Primary Outcome: The Changes in Vestibular Migraine Frequency

The main results revealed that valproic acid (SMD −1.61, 95% CI −2.69, −0.54), propranolol (SMD −1.36, 95% CI −2.55, −0.17), and venlafaxine (SMD −1.25, 95% CI −2.32, −0.18) were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups (Table 2, Figs. 2, 3). With regard to clinical applicability, we calculated the probability of relative superiority of individual treatments compared with others

Fig. 1 Selection of studies for inclusion in the present network meta-analysis
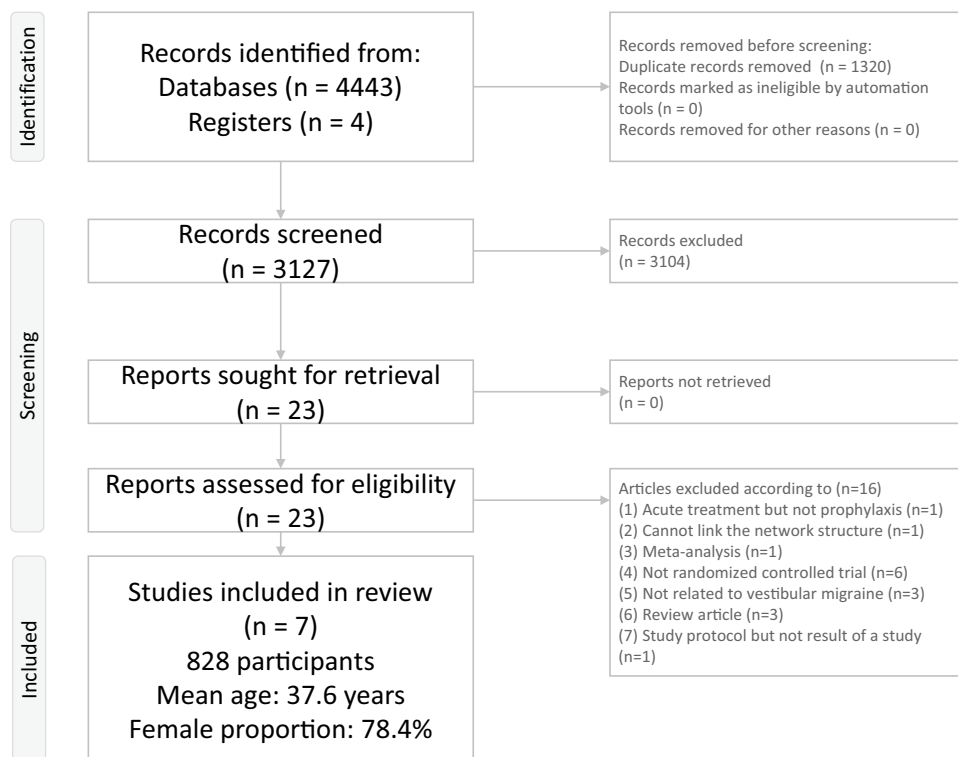
Table 1 Characteristics of the included studies

| Study, year	Comparison	No. of subjects	Mean age, years	Female (%)	Study duration (weeks)	Country
Sun et al., 2022 [54]	Resistance exercise	145	33.1 ± 5.9	81.4	12	China
	Relaxation control (treatment as usual)	141	34.5 ± 6.3	83.0		
Qi et al., 2020 [52]	Probiotic L. casei Shirota	103	32.0	86.4	16	China
	Placebo	101	33.0	84.2		
Bayer et al., 2019 [11]	95 mg/day metoprolol	65	44.4 ± 14.2	66.2	24	Germany
	Placebo	65	42.8 ± 14.3	55.4		
Liu et al., 2017 [51]	37.5 mg/day venlafaxine	23	53.2 ± 15.6	69.6	12	China
	10 mg/day flunarizine HS	22	51.5 ± 15.4	63.6		
	1000 mg/day valproic acid	20	52.4 ± 16.0	75.0		
Salviz et al., 2016 [53]	160 mg/day propranolol	33	38.0	93.9	12	Turkey
	150 mg/day venlafaxine	31	42.0	90.3		
Yuan et al., 2016 [55]	10 mg/day flunarizine HS	13	45.3 ± 6.8	85.2	12	China
	Treatment as usual	14				
Lepcha et al., 2014 [50]	10 mg/day flunarizine HS	26	NA	61.5	12	India
	Treatment as usual	26		69.2		

NA not available
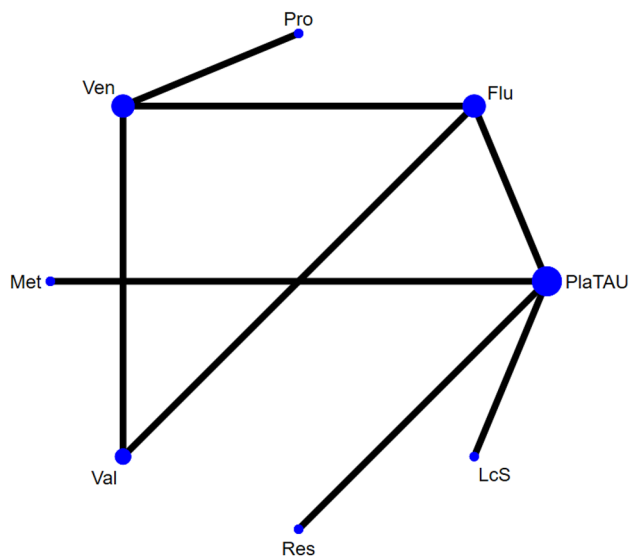
Fig. 2 Overall network structure of the current network meta-analysis for the primary outcome of changes in vestibular migraine frequency. The lines between nodes represent direct comparisons in various trials, and the size of each circle is proportional to the number of participants receiving each specific treatment. The thickness of the lines is proportional to the number of trials connected to the network. *Flu* flunarizine, *LcS* probiotic of L. casei Shirota, *Met* metoprolol, *PlaTAU* placebo or treatment as usual, *Pro* propranolol, *Res* resistance exercise, *Val* valproic acid, *Ven* venlafaxine

according to the SUCRA analysis. To be specific, valproic acid yielded the most decreased vestibular migraine frequency among all interventions (ESM Table 3A).

Subgroup analysis based on RCTs of pharmacological treatment revealed similar findings. Specifically, valproic

acid (SMD −1.61, 95% CI −2.73, −0.50), propranolol (SMD −1.36, 95% CI −2.60, −0.12), and venlafaxine (SMD −1.25, 95% CI −2.36, −0.14) were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups (ESM Table 4A, ESM Fig. 1A, and ESM Fig. 2B). Similarly, in consideration of the clinically relative superiority of efficacy, valproic acid yielded the most decreased vestibular migraine frequency among all interventions according to the SUCRA results (ESM Table 3B).

The test of similarity revealed that there was no significant difference in the changes of vestibular migraine frequency between the 'RCT with placebo' and 'RCT with controls' groups ($p = 0.101$) (ESM Fig. 2A).

3.3 Secondary Outcome: Changes of Vestibular Migraine Severity

The main result of the NMA revealed that none of the investigated treatments were associated with significantly different improvements in vestibular migraine severity compared with the placebo/control groups (ESM Table 4B, ESM Table 3C, ESM Fig. 1B, and ESM Fig. 2C).

3.4 Acceptability with Respect to the Dropout Rate

The main result of the NMA revealed that none of the investigated treatments were associated with significantly different dropout rates compared with the placebo/control groups (ESM Table 4C, ESM Table 3D, ESM Fig. 1C, and ESM Fig. 2D).

Table 2 League table of the primary outcome: changes in vestibular migraine frequency
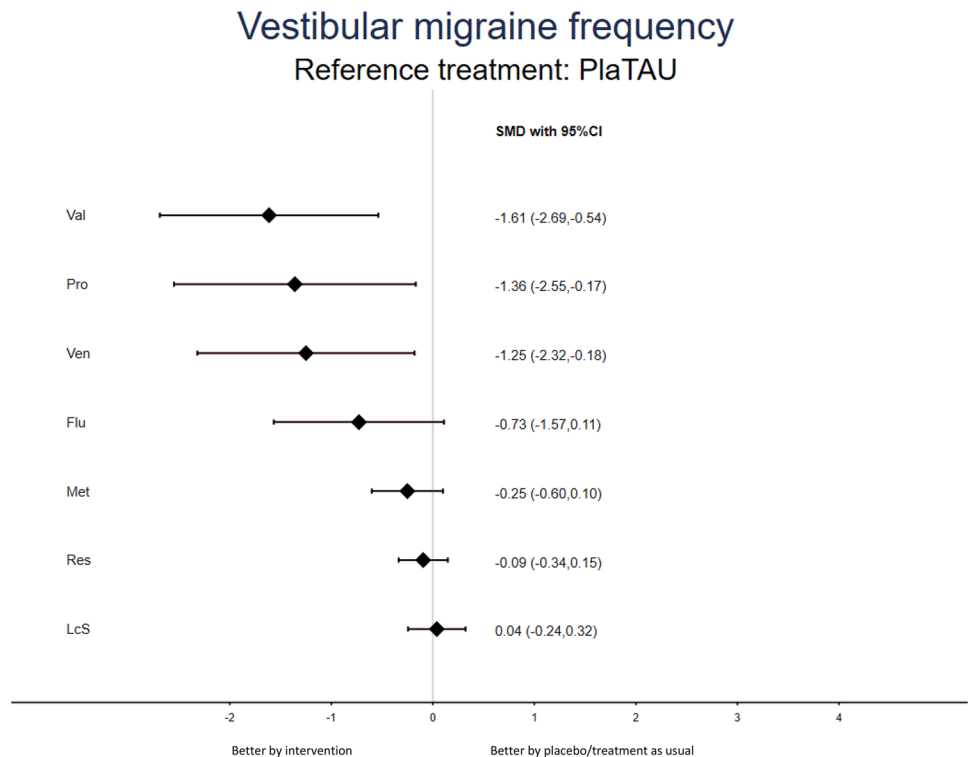
Val							
Val		−0.36 (−0.97, 0.24)	**−0.89 (−1.51, −0.26)**				
−0.25 (−1.03, 0.53)	Pro	−0.11 (−0.60, 0.38)					
−0.36 (−0.97, 0.24)	−0.11 (−0.60, 0.38)	Ven	−0.52 (−1.11, 0.07)				
−0.88 (−1.52, −0.25)	−0.63 (−1.42, 0.16)	−0.52 (−1.13, 0.08)	Flu			−0.73 (−1.51, 0.06)	
−1.36 (−2.47, −0.25)	−1.11 (−2.33, 0.11)	−1.00 (−2.10, 0.10)	−0.48 (−1.36, 0.41)	Met		−0.25 (−0.60, 0.09)	
−1.52 (−2.60, −0.44)	**−1.26 (−2.45, −0.08)**	**−1.15 (−2.22, −0.09)**	−0.63 (−1.48, 0.21)	−0.16 (−0.57, 0.26)	Res	−0.10 (−0.33, 0.14)	
−1.61 (−2.69, −0.54)	**−1.36 (−2.55, −0.17)**	**−1.25 (−2.32, −0.18)**	−0.73 (−1.57, 0.11)	−0.25 (−0.60, 0.10)	−0.09 (−0.34, 0.15)	PlaTAU	−0.04 (−0.31, 0.24)
−1.65 (−2.74, −0.56)	**−1.40 (−2.60, −0.20)**	**−1.29 (−2.37, −0.21)**	−0.77 (−1.63, 0.09)	−0.29 (−0.73, 0.15)	−0.13 (−0.49, 0.23)	−0.04 (−0.32, 0.24)	LcS

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the outcome of improvement of vestibular migraine frequency. Interventions are reported in order of mean ranking of vestibular migraine frequency improvement, and outcomes are expressed as SMD (95% CIs). For the pairwise meta-analyses, an SMD of <0 indicates that the treatment specified in the row had more improvement than that specified in the column. For the NMA, an SMD of <0 indicates that the treatment specified in the column had more improvement than that specified in the row

Bolded values indicate statistical significance

CIs confidence intervals, *Flu* flunarizine, *LcS* probiotic of L. casei Shirota, *Met* metoprolol, *NMA* network meta-analysis, *PlaTAU* placebo or treatment as usual, *Pro* propranolol, *Res* resistance exercise, *SMD* standardized mean difference, *Val* valproic acid, *Ven* venlafaxine

Fig. 3 Forest plot of the primary outcome—changes in vestibular migraine frequency. When the effect size was <0 (presented as the SMD), the specified treatment yielded a better improvement in vestibular migraine frequency than the control group. *CI* confidence interval, *Flu* flunarizine, *LcS* probiotic of L. casei Shirota, *Met* metoprolol, *PlaTAU* placebo or treatment as usual, *Pro* propranolol, *Res* resistance exercise, *SMD* standardized mean difference, *Val* valproic acid, *Ven* venlafaxine

Vestibular migraine frequency
Reference treatment: PlaTAU

SMD with 95%CI

	SMD with 95%CI
Val	-1.61 (-2.69,-0.54)
Pro	-1.36 (-2.55,-0.17)
Ven	-1.25 (-2.32,-0.18)
Flu	-0.73 (-1.57,0.11)
Met	-0.25 (-0.60,0.10)
Res	-0.09 (-0.34,0.15)
LcS	0.04 (-0.24,0.32)

Better by intervention   Better by placebo/treatment as usual

3.5 Safety Profile with Respect to Any Adverse Effect Rate

The main result of the NMA revealed that none of the investigated treatments were associated with significantly different adverse effect rates compared with the placebo/control groups (ESM Table 4D, ESM Table 3E, ESM Fig. 1D, and ESM Fig. 2E).

3.6 Risk of Bias and Publication Bias

We found that 75.5% (37/49 items), 8.2% (4/49 items), and 16.3% (8/49 items) of the included studies had low, unclear, and high risks of bias, respectively. The vague reporting of allocation concealment and the blindness of the participants/investigator contributed to the risk of bias (ESM Fig. 3A, B).

Funnel plots of publication bias across the included studies (ESM Figs. 4A–H) revealed general symmetry, and the results of the Egger's test indicated no significant publication bias among the articles included in the NMA. The aforementioned test of similarity revealed insignificant differences ($p = 0.101$) (ESM Fig. 2A). Furthermore, in general, the current NMA does not exhibit inconsistency, whether local inconsistency (assessed using the loop-specific approach and node-splitting method) or global inconsistency (assessed using the design-by-treatment method), therefore there was no evidence to refute the assumption of similarity/transitivity/consistency (ESM Table 5, ESM Table 6). No significant heterogeneity was detected by tau value (ESM Table 7). The GRADE rating revealed that the quality of evidence for most comparisons in the current NMA ranged from low to medium (ESM Table 8).

4 Discussion

The main finding of the present NMA is that most brain-acting regimens (i.e., valproic acid, propranolol, and venlafaxine) were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups. Furthermore, among all the investigated pharmacologic/non-pharmacologic treatments, valproic acid yielded the most decreased vestibular migraine frequency among all the interventions. In addition, most pharmacologic/non-pharmacologic treatments were associated with acceptability and safety profiles similar to those of the placebo/control groups.

Our NMA observed that most brain-acting regimens (i.e., valproic acid [51], propranolol [53], and venlafaxine [51, 53]) were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups. Valproic acid was associated with the most decreased vestibular migraine frequency among all

interventions. This finding was consistent with our previous large-scale NMA regarding ordinary migraine [8], in which we observed that high-dose melatonin, valproic acid, and topiramate were all associated with significant improvement in ordinary migraine frequency in comparison with placebo controls. There have been arguments regarding the different treatment efficacies of individual pharmacological treatments for ordinary migraine and vestibular migraine. Considering the main findings of these two NMAs, we noted similar and different parts. Specifically, the anticonvulsant valproic acid was effective against both vestibular migraine and migraine. This beneficial effect could be derived from the physiopathology of vestibular migraine that the asymmetrical activation of the vestibular nucleus, which is mediated by balanced glutamate and gamma-aminobutyric acid (GABA), is associated with vertigo symptoms in vestibular migraine [56]. Therefore, the prescription of valproic acid, which would inhibit N-methyl-D-aspartate receptors and modulate intra-brain GABA levels, would contribute to its efficacy in vestibular migraine management [10].

Another important finding of the current NMA was that the other two brain-acting regimens (i.e., propranolol [53] and venlafaxine [51]) were both significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups. Venlafaxine, a regimen with serotonergic effects, was only effective in vestibular migraine but not in ordinary migraine [8]. These different findings might be supported by a previous cross-sectional analytic study that vestibular migraine patients are significantly more anxious and agoraphobic than ordinary migraine patients at baseline [57]. Similarly, in another important trial, the prescription of serotonergic regimens in patients with dizziness, either with an otogenic or pure psychogenic etiology, resulted in significant improvement in both anxiety and dizziness severity [58]. Therefore, theoretically, a venlafaxine prescription would be effective for vestibular management. In contrast, propranolol, classified as a competitive non-cardioselective sympatholytic β-blocker, was only effective in vestibular migraine and not in ordinary migraine [8]. Propranolol, which can cross the blood–brain barrier, acts not only on the β-adrenergic receptor but also weakly on certain serotonin receptors, such as 5-HT1A, 5-HT1B, and 5-HT2B [59], thus exerting anxiolytic effects [59]. According to a previous clinical trial, uncontrolled comorbid anxiety is a risk factor for reduced treatment response to vestibular migraine [60]. Considering the above evidence together, we hypothesized that the beneficial effects of venlafaxine and propranolol on vestibular migraine management might be derived from reduced comorbid anxiety. However, since the overall included RCTs were relatively few and the evidences of the efficacy of valproate, propranolol, and venlafaxine versus the placebo/control group mainly came from an indirect comparison, the results of the current NMA

are preliminary. Furthermore, the evidence from an indirect comparison would be weaker than those from direct evidence, therefore the power of an indirect comparison would be relatively small. Therefore, we may need future large-scale RCTs to form a direct comparison between the aforementioned treatments so that we might achieve more conclusive evidence [61, 62]. In addition, although no significant heterogeneity was detected via statistical examination or in the overall demographic data of the subjects within the recruited RCTs, some analyses in our NMA might be limited by potential heterogeneity between studies. With regard to the treatment efficacy of resistance exercise [54], probiotics [52], metoprolol [11], and flunarizine [50, 55], the statistical insignificance might have resulted from the low sample size and low power due to the indirect comparison. Finally, although some RCTs of cinnarizine, clonazepam, topiramate, amitriptyline, triptans, or monoclonal antibodies in ordinary migraine management have been conducted, we did not include the aforementioned treatments in this NMA due to a lack of RCTs of those regimens in vestibular migraine management.

Our NMA had some limitations that need to be addressed. First, some analyses in our NMA were limited by potential heterogeneity between studies with respect to participant characteristics such as underlying diseases, concomitant medication, age, heterogeneous diagnostic criteria, and trial duration. Second, some of the included studies had small sample sizes, which may have resulted in less robust quantitative findings. Third, some of the included RCTs did not apply placebo controls, and a placebo effect could have affected their findings. Fourth, as previously mentioned, we did not include the treatment of cinnarizine, metoprolol, clonazepam, topiramate, amitriptyline, triptans, or monoclonal antibodies due to the lack of RCTs of these regimens in vestibular migraine management. Finally, most RCTs in the current NMA had relatively short study durations (mean follow-up duration 14.9 weeks). Further studies with longer study periods are required.

5 Conclusion

The present NMA demonstrated that most brain-acting regimens (i.e., valproic acid, propranolol, and venlafaxine) were significantly associated with better improvement in vestibular migraine frequency than the placebo/control groups. Furthermore, among all the investigated pharmacologic/non-pharmacologic treatments, valproic acid was associated with the most decreased vestibular migraine frequency among all interventions. In addition, most pharmacologic/non-pharmacologic treatments were associated with acceptability and safety profiles similar to those of the placebo/control groups. Because of the limitations of the small sample sizes, our

findings imply the need for future large-scale RCTs to support or refute the findings of the current NMA.

Declarations

Consent to participate Not applicable.

Consent for publication Not applicable.

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