BRAIN
REVIEW ARTICLE

Vestibular migraine treatment: a comprehensive practical review

Duncan Smyth,[1] Zelie Britton,[1] Louisa Murdin,[2,3] Qadeer Arshad[4] and Diego Kaski[1]

Vestibular migraine is an underdiagnosed but increasingly recognized neurological condition that causes episodic vertigo associated with other features of migraine. It is now thought to be the most common cause of spontaneous (non-positional) episodic vertigo, affecting up to 1% of the population. A meta-analysis of preventative treatments for vestibular migraine was published in 2021, but the authors were unable to establish a preferred treatment strategy due to low quality of evidence and heterogeneity of study design and outcome reporting. Therefore, there remains a clinical need for pragmatic management guidelines specific to vestibular migraine using the available evidence. Here, we provide a practical review utilizing a systematic qualitative assessment of the evidence for abortive and preventative interventions in adults. The overall evidence base for vestibular migraine treatment is of low quality. Nevertheless, we provide practical treatment recommendations based on the available evidence and our experience to help guide clinicians treating patients with vestibular migraine. We also discuss how future clinical trials could be designed to improve the quality of evidence in this condition.

1 Department of Neuro-Otology, National Hospital for Neurology and Neurosurgery, London, UK
2 Department of Ear, Nose and Throat, Guy's and St Thomas' NHS Foundation Trust, London, UK
3 Ear Institute, Faculty of Brain Sciences, University College London, London, UK
4 Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, UK

Correspondence to: Dr Diego Kaski
Department of Neuro-Otology
National Hospital for Neurology and Neurosurgery
Queen Square, London WC1N 3BG, UK
E-mail: d.kaski@ucl.ac.uk

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Introduction

Vestibular migraine (VM) is an underdiagnosed but increasingly recognized condition that causes episodic vertigo, often accompanied by headache. A condition first clearly described by Boenheim in 1917,[1] it is now thought to be the most common cause of spontaneous (non-positional) episodic vertigo, affecting between 1% and 2.7% of the general population,[2,3] 11% of patients in specialized dizziness clinics[4] and 13% of patients in headache clinics.[5] Previously known variously as 'migrainous vertigo', 'migraine-associated vertigo', 'migraine-associated dizziness', 'migraine-anxiety-associated dizziness' and 'migraine-related vestibulopathy', vestibular migraine has been accepted by the International Classification of Headache Disorders (ICHD) as the unifying term that identifies both the vestibular and migrainous symptoms.

The clinical presentation of vestibular migraine is diverse. Episodes of dizziness usually last between 5 min and 72 h, although shorter and longer episodes have been reported.[6] Vestibular symptoms can mimic benign paroxysmal positional vertigo,[7] and prominent auditory symptoms with overlap with Ménière's disease have been reported.[8,9] Episodes are often, but not invariably, accompanied by other symptoms of migraine, including migrainous headache, photophobia, phonophobia and visual aura. Neurological examination is classically unremarkable, but during acute attacks

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can reveal spontaneous or positional nystagmus in the majority of patients,[7,10–13] and some studies have reported mild abnormalities of semicircular canal function and eye movements interictally.[7,10,14–18] The current diagnostic criteria, first proposed by Neuhauser *et al.*[4] and ratified by the International Headache Society and the committee for the International Classification of Vestibular Disorders (ICVD) of the Bárány Society,[6] mandate a history of migraine and the temporal overlap of vestibular and migrainous symptoms in at least 50% of episodes, and allow for the possibility of probable vestibular migraine (see Table 1). Importantly for a disease without an objective diagnostic gold standard, these criteria have been shown to be reliable on repeated assessments over a 9-year period.[9]

The pathophysiology of vestibular migraine is incompletely understood. As with migraine, there is a significant female preponderance[4,19] for reasons not well explained. Both environmental and genetic factors are likely to be important,[20,21] and recent familial studies have suggested possible loci of interest at 5q35,[22] 11q (with reduced penetrance in men)[23] and 22q12.[24] One proposed mechanism for episodes is hypoperfusion of the inner ear during migrainous attacks secondary to vasospasm resulting in vertiginous symptoms, a theory that is supported by the occasional association of migraine with sudden sensorineural hearing loss[25] and the observation that migraine is a risk factor for stroke[26,27]; however, cochlear symptoms are certainly not a universal feature. Alternatively, episodes may be due to sensitization and activation of the trigeminovascular system leading to release of the pro-inflammatory neuropeptides substance P and calcitonin gene-related peptide (CGRP), which has connections with brain areas associated with processing of nociceptive information as well as thalamic and vestibular-associated cortices.[28] Neuroimaging studies support the hypothesis that there are specific abnormalities in the structure and activity of the vestibulo-thalamo-cortical pathway in vestibular migraine.[29,30]

Table 1 Bárány Society/International Headache Society criteria for vestibular migraine

Vestibular Migraine	Probable Vestibular Migraine
A. At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h	**A.** At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h
B. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)	**B.** Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history or migraine features during the episode)
C. One or more migraine features with at least 50% of the vestibular episodes: • headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity • photophobia and phonophobia • visual aura	**C.** Not better accounted for by another vestibular or ICHD diagnosis
D. Not better accounted for by another vestibular or ICHD diagnosis	

Due to a paucity of data on the management of vestibular migraine specifically, treatment recommendations have generally been extrapolated from studies on other forms of migraine. Pharmacological options for acute migraine include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), antiemetics and triptans.[31] Prophylactic treatment options include beta-blockers (propranolol, metoprolol), calcium channel blockers (for example, flunarizine), antiepileptic drugs (topiramate, sodium valproate), antidepressants (amitriptyline, nortriptyline, venlafaxine), antiserotonergic drugs (pizotifen), antihypertensives (candesartan, lisinopril) and monoclonal antibodies against CGRP (erenumab, fremanezumab, galcanezumab). Supplements (co-enzyme Q10, magnesium and riboflavin), greater occipital nerve block, botulinum toxin, external trigeminal nerve stimulation (eTNS), single transcranial magnetic stimulation and non-invasive vagus nerve stimulation (nVNS) are recommended by the British Association for the Study of Headache.[31] Acupuncture may be helpful for some patients.[32] A Cochrane review in 2015 that set out to identify effective pharmacological agents for the prevention of vestibular migraine failed to identify any completed study that met the strict inclusion criteria required for Cochrane reviews.[33] A review and meta-analysis of preventive treatments for vestibular migraine was published in 2021,[34] but the authors were unable to establish a preferred treatment strategy due to low quality of evidence and heterogeneity of study design and outcome reporting.

As current migraine treatment guidelines are based on work that did not assess the efficacy of interventions to control vestibular symptoms, there remains a clinical need for pragmatic management guidelines specific to vestibular migraine using the available evidence. Considering this, we felt that performing another meta-analysis would not be of practical utility given such a small number of appropriate studies. Equally, a narrative review would likely include publications at risk of serious bias due to poor study quality and significant heterogeneity. Thus, while others have provided comprehensive systematic reviews and meta-analyses of vestibular migraine treatment,[33,34] here we sought to offer a practical, clinically oriented review utilizing a systematic qualitative assessment of the evidence for each treatment option, upon which we offer treatment recommendations.

Search strategy

The initial search was performed on 24 November 2020 and the following sources were searched: Ovid AMED/Embase Classic (1947 to 2020 November 24), Embase/Emcare (1995 to present), Ovid MEDLINE (and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2015 to 24 November 2020), Scopus, Web of Science, CINAHL and the Cochrane Database of Systematic Reviews. A repeat search was performed on 6 January 2022. To account for the fact that vestibular migraine is a relatively recent term, the outdated terms 'migrainous vertigo', 'migraine-associated vertigo', 'migraine-associated dizziness', 'migraine-anxiety-associated dizziness' and 'migraine-related vestibulopathy' were included in the search strategy in addition to 'vestibular migraine'. Only studies pertaining to adults (>18 years) were included. Potentially relevant studies were selected, and reference lists for included studies were also searched to find additional studies that met the inclusion criteria. The results of the search and study selection are shown in Supplementary Fig. 1. Details of study selection and inclusion criteria and selection of outcome measures are provided in Supplementary Material.

Abortive treatment

There have been four studies on abortive treatment for an acute attack of VM, which are detailed in Supplementary Table 1. Despite their widespread use in migraine headache, there have only been two studies of triptans in VM. The first was a randomized crossover trial[35] that compared zolmitriptan 2.5 mg with placebo and aimed to enrol 50 patients; however, only 17 VM attacks were included in 10 patients, and thus the study did not produce any significant results. Three of eight patients receiving zolmitriptan reported improvement from moderate or severe vertigo to no or mild vertigo, compared with two of nine receiving placebo. Even fewer patients had attacks involving headache, with one of five patients receiving zolmitriptan reporting improvement in headache compared with two of five receiving placebo. A randomized controlled trial (RCT) comparing rizatriptan 10 mg with placebo for treatment of acute vestibular migraine has now been completed, with preliminary results published on ClinicalTrials.gov.[36] One hundred and thirty-four patients underwent treatment, having had at least two VM episodes in the preceding 12 months. Eighty-nine patients were randomized to rizatriptan (151 attacks with moderate or severe vestibular symptoms) and 45 to placebo (89 attacks with moderate or severe vestibular symptoms). Both primary outcomes were negative: for the symptom of vertigo, 48% of rizatriptan-treated episodes reduced from 'moderate/severe' to 'none/mild' at 1 h compared with 56% of placebo-treated episodes ($P < 0.33$), and for dizziness/unsteadiness, the corresponding figures were 19% and 12%, respectively ($P < 0.18$). Some symptoms but not others were found to be better with rizatriptan at 24 h, and there was also slightly higher mean patient satisfaction with rizatriptan at 48 h; however, the majority of the 18 secondary efficacy measures were also negative. Patients treated with rizatriptan reported higher rates of fatigue (49% versus 16%) and sleepiness (57% versus 24%). These studies are consistent with our clinical experience that triptans are less effective for acute vertigo attacks than headache attacks.

Various forms of neuromodulation can be used for both acute and prophylactic treatment of migraine[37] and two have shown initial promise in VM but require further evaluation. One small retrospective before-and-after study used nVNS in 14 patients with an acute attack of VM.[38] Using visual analogue scales (VAS), mean self-reported vertigo severity was 5.2 (out of 10) before treatment and 3.1 at 15 min after treatment, and mean headache severity (in the five patients with headache) was 6 before treatment and 2.4 after treatment. A similar study from the same authors used eTNS in 19 patients and found a reduction in mean VAS vertigo severity from 6.6 before treatment to 2.7 at 15 min after treatment, and a reduction in mean VAS headache severity ($n = 14$) from 4.8 before treatment to 1.4 after treatment.[39] No significant side effects were reported in either the nVNS or eTNS studies, consistent with the favourable safety profile in migraine.[37] The use of neuromodulation may be limited by the need for specialist equipment and training as well as cost, although the UK National Institute for Health and Care Excellence (NICE) has determined nVNS to be cost-effective in some cases of cluster headache depending on existing medication use.[40] Importantly, however, the efficacy beyond placebo effect in VM remains unproven because both studies were uncontrolled with a simple before-and-after comparison in a self-selecting group of patients (those who had chosen to attend the clinic during an acute attack). There are no data regarding sustained effects against a control and over repeated treatments.

Authors' comments

There is little evidence to support triptan use for acute VM attacks for vertigo and dizziness alone, although they are established as headache treatments. Non-invasive vagus nerve stimulation and external trigeminal nerve stimulation may reduce vertigo symptoms at 15 min post-treatment, but longer-term benefits are unknown and devices are not readily accessible.

Preventative treatment

Details of the 23 studies on prophylactic treatment are contained in Supplementary Table 2.

Pharmacological treatment

Beta-blockers

Beta-blockers are commonly used for migraine treatment, although the mechanism of action in migraine is incompletely understood.[41] There were four studies of propranolol in VM and one of metoprolol. Propranolol was associated with reductions in vertigo frequency and severity using before-and-after comparisons. Doses in the studies varied: 40 mg twice daily for weight <60 kg and 60 mg twice daily for weight >60 kg,[42] up to 80 mg twice daily,[43] 10 mg once daily[44] and 40 mg and 80 mg once daily (two different treatment arms).[45] A retrospective, uncontrolled study[42] followed 38 patients prescribed propranolol 80–120 mg daily for between 6 and 32 months. Due to the variable follow-up, the authors attempted to standardize the duration of symptoms by converting symptom frequency to 1 year. The mean 'annual duration of symptoms' was 115 days before treatment and 13 days after treatment ($P < 0.001$); however, this was an extrapolation and likely to have been inaccurate. Mean vertigo severity (VAS 0–10) reduced from 7.52 to 1.34 ($P < 0.001$) and the dizziness handicap inventory (DHI), a well-validated measure of the impact of dizziness disability, reduced from 50.21 to 9.31 ($P < 0.001$). The vertigo symptom scale (VSS) and a quality-of-life measure (vestibular activities of daily living scale, VADL) were also lower after treatment. An unblinded RCT comparing propranolol 40–160 mg daily ($n = 26$) and venlafaxine 37.5–150 mg daily ($n = 26$) for 4 months found no significant differences between the two treatments, except that propranolol was inferior for depressive symptoms.[43] A before-and-after analysis was also performed, and patients receiving propranolol showed marked reductions in mean monthly vertigo frequency (from 12.6 to 1.9, $P < 0.001$), DHI (55.8–31.3, $P < 0.001$), VAS vertigo severity (7.3–2.1, $P < 0.001$) and the Beck Anxiety Inventory (BAI). Two small observational studies compared outcomes in patients receiving multiple treatments including propranolol.[44,45] These studies found improvements in subjective measures of vertigo and headache severity from pre- to post-treatment but were underpowered to detect between-group differences. Propranolol has never been compared to a placebo (or a control group without placebo) in VM and thus some of the benefits seen in the studies could be due to this confound.

The first multicentre, double-blind RCT in VM treatment was published in 2019, comparing controlled-release metoprolol 95 mg daily with placebo over 6 months.[46] Recruitment was slower than expected, with 130 patients eventually randomized (the planned sample size was 266), meaning the planned primary per protocol end point analysis could not be completed. Mean monthly vertigo frequency decreased from 4.2 to 2.8 attacks per month between months 4 and 6 in the metoprolol group and from 4.5 to 3.1

attacks per month in the placebo group ($P = 0.696$). Mean monthly migraine headache days over months 4–6 were also similar between the two groups (2.4 in metoprolol group versus 2.5 in placebo group, $P = 0.904$). An averaged DHI remained unchanged in both groups. No superiority of metoprolol over placebo was found for any of the outcome measures. Despite participant numbers being fewer than anticipated, the confidence interval for the incidence rate ratio was narrow, indicating that a large treatment effect was not likely.

Beta-blockers were generally well-tolerated, although in two studies approximately 12% of patients discontinued medication[43,46] compared with 7% for placebo in one of these studies.[46] One of the multiple-treatment-arm studies that used a very low daily dose of propranolol (10 mg) observed a high dropout of patients from other treatment arms, but the four patients in the propranolol group were adherent.[44] Two studies on beta-blockers did not report on side effects.[42,45]

Authors' comments

Propranolol was seen to improve headache and vertigo severity in before-and-after studies. Beta-blockers are generally well tolerated by patients with good adherence rates and for this reason are commonly used in VM prophylaxis. However, in the most robust study of VM treatment metoprolol did not reduce vertigo frequency or dizziness handicap compared to placebo.

Calcium channel blockers

The non-selective diphenylpiperazine calcium channel blockers (flunarizine, lomerizine, cinnarizine) have been used in migraine since the 1980s.[47] This particular class has widespread pharmacodynamic effects: flunarizine and cinnarizine also antagonize H1 histamine[48] and D2 dopamine receptors,[49] and lomerizine antagonizes 5HT-2A receptors.[50] Verapamil was also used historically for migraine prophylaxis,[51] although now is much more commonly used for cluster headache. Four studies looked exclusively at calcium-channel blockers and four multiple-treatment-arm studies included a calcium-channel blocker arm.

Lomerizine was examined in one retrospective uncontrolled study,[52] where patients were treated initially with dietary advice alone, and lomerizine 10 mg daily was commenced in addition if the dietary advice was unsuccessful or had been tried previously. Treatment duration and follow-up was variable (personal correspondence with author), and there was no comparator group. Nineteen of the 22 patients treated with lomerizine reported at least 75% reduction in vertigo frequency.

Cinnarizine was examined in two studies. The first was a retrospective, uncontrolled before-and-after study of 24 patients with VM and 16 patients with migraine with brainstem aura treated with 75 mg daily for 3 months and was primarily focused on headache outcomes.[53] Baseline attack frequency was relatively low in comparison to other studies. For the VM patients, mean monthly vertigo frequency improved from 3.37 to 0.42 attacks per month ($P < 0.001$), and monthly headache frequency improved from 3.92 to 0.75 attacks per month ($P < 0.001$). There was also a marked reduction in mean headache duration (23.58–2.58, $P < 0.001$) and severity (8 to 1 on a VAS 0–10, $P < 0.001$). The second study was a prospective observational study that followed 22 patients given a combination of cinnarizine 20 mg and diphenhydramine 40 mg, twice daily every second month (i.e. 'month on, month off') for 6 months, plus dietary and lifestyle advice (which was not explained in detail).[54] These patients were compared to a control group of 11 patients given dietary and lifestyle advice alone, without placebo. Patients had relatively mild disease (mean vertigo and headache attack frequency was less than once monthly at baseline) and patients receiving the study medication had more frequent attacks at baseline. The mean reduction in 6-monthly vertigo frequency was 3.2 attacks in the treatment group compared to 1.3 in the control group [mean difference (MD) 1.9, $P = 0.143$] and the mean reduction in 6-monthly headache frequency was 2.6 compared to 0.6 (MD 2.0, $P = 0.10$).

Flunarizine has long been proposed as a treatment for 'vestibular vertigo' of any cause, perhaps accounting for its use in VM also.[55] There were four studies of flunarizine. Lepcha and colleagues performed an open-label randomized trial of 52 patients with VM, half of whom were given flunarizine 10 mg daily for 12 weeks.[56] All patients were given 'as needed' paracetamol and betahistine and were instructed to perform vestibular exercises; however, the control group did not receive a placebo. In the post-intervention analysis, 88% of the flunarizine group compared to 52% of the control group reported having 'low vertigo frequency' (2–3 attacks or less per 3 months) as per a unique 6-point Likert scale ($P = 0.01$), and 88% of the flunarizine group reported a 'marked improvement' compared to 61% of the control group, using another unique scale ($P = 0.046$). However, the study did not report outcome measures at baseline, and multiple scale points were grouped together arbitrarily to determine 'low frequency' and 'marked improvement' and it was not clear whether adjustment to the significance level for multiple comparisons was made. There were no significant differences in headache measures between the two groups. A single-blinded quasi-randomized study systematically allocated 75 participants to either flunarizine 10 mg daily, venlafaxine 37.5 mg daily or sodium valproate 500 mg twice daily.[57] In a before-and-after analysis of the flunarizine group, there were small improvements in subjective VAS vertigo severity (6.4–5.9, $P = 0.03$), monthly vertigo frequency (5.0–4.2 attacks per month, $P = 0.057$) and DHI (46.6–39.8, $P = 0.019$). Two small observational multiple-treatment-arm before-and-after studies (mentioned in 'Beta-blockers' previously) also included flunarizine.[44,45] In one of these studies, of the four patients receiving flunarizine, two failed to attend the follow-up appointment and one was non-adherent to the medication.[44] In the other, a before-and-after analysis showed reductions in subjective measures of vertigo and headache severity in 11 patients.[45]

Three patients were treated with verapamil 120 mg twice daily in a retrospective multiple-arm study.[58] The treatment duration of verapamil-treated patients was unclear. On average, DHI reduced by a small amount (9.3 points) from pre- to post-treatment in the three patients.

In summary, lomerizine 10 mg daily[52] and cinnarizine 75 mg daily[53] were reported to reduce headache and vertigo severity and frequency, but when lower doses of cinnarizine (40 mg daily) were compared to a control group, no difference was seen.[54] Flunarizine 10 mg daily was reported to reduce vertigo severity,[45,56,57] vertigo frequency,[56] DHI[57] and headache severity.[45] While the study by Lepcha and colleagues had some methodological issues, it did contain a control group (without placebo),[56] meaning that the evidence for flunarizine is slightly stronger than for other VM treatments. However, calcium channel blockers had a higher rate of reported adverse effects than beta-blockers in the majority of studies: 24% of patients experienced side effects compared with 9% in the control group in one study,[56] and 27% experienced side effects in another.[57] The rate of side effects reported with cinnarizine were 22.5%[53] and between 32 and 68% (unclear reporting).[54] Side effects commonly reported included dry mouth,

blurred vision, somnolence, weight gain, nausea and acne. There were no reports of drug-induced parkinsonism, although study durations were typically short (3–6 months) and this remains a concern with long-term use. It is possible that the benefit of this group of calcium-channel blockers in VM is at least partly attributable to their antihistaminergic (flunarizine, cinnarizine) or antiserotonergic (lomerizine) effects. Importantly, flunarizine may take up to 8 weeks to reach a steady state in plasma, indicating that studies may not have allowed sufficient time for maximal effect to be seen.

Authors' comments

There is some evidence that flunarizine reduces vertigo attack frequency and severity in VM. Cinnarizine and lomerizine may also be of benefit in VM, although the evidence for these is less than for flunarizine. These drugs commonly cause side effects; however, discontinuation rates are low. There is no evidence to support verapamil use in VM.

Antiepileptic drugs

There were studies of lamotrigine, topiramate and sodium valproate in VM. Vestibular symptoms in VM were thought to be a form of migraine aura in previous pathophysiological models,[14] which led to some interest in lamotrigine for VM prophylaxis due to its role in treatment of migraine aura, which may be mediated through inhibition of cortical spreading depression.[59] There has been one small retrospective, uncontrolled before-and-after study of lamotrigine, where 19 patients received 100 mg daily for between 3 and 4 months.[60] Mean vertigo frequency reduced from 18.2 to 5.4 attacks per month ($P < 0.001$) and monthly headache frequency reduced from 8.7 to 4.4 (reported as 'not significant') over the course of the study. No side effects were reported by the participants, which is concordant with our clinical experience that lamotrigine is generally well-tolerated.

Sodium valproate is an established preventative treatment for migraine headache[61] and acts on multiple neurotransmitters that may have relevance in migraine.[41] It has only been examined in multiple-arm studies in VM. In one study, 25 patients receiving sodium valproate 500 mg twice daily were compared to groups of the same size receiving flunarizine and venlafaxine.[57] A before-and-after analysis of the sodium valproate group found that monthly vertigo frequency improved from 5.1 to 2.4 attacks per month ($P < 0.05$) and there was also an improvement in DHI (46.8–38.6, $P = 0.02$), although a VAS for vertigo symptoms was similar pre- and post-treatment (5.8–5.3, $P = 0.27$). Sixteen percent of patients reported non-serious side effects (nausea, insomnia, palpitations, lethargy and indigestion). Sodium valproate can cause weight gain, a reason why many patients may choose to avoid or stop the drug. Moreover, sodium valproate is known to be teratogenic,[62] and appropriate caution must accordingly be used when prescribing to young women, although not all studies of valproate in VM have excluded women of childbearing age.[57]

Like sodium valproate, topiramate has multiple mechanisms of action which may contribute to its antimigraine effect.[41] In VM it was examined in an unblinded trial of 30 patients, where participants were randomized into high dose (50 mg twice daily) and low dose (25 mg twice daily) groups for 24 weeks.[63] While purporting to be a randomized trial, the primary aim of the study was to compare vertigo and headache outcome measures before and after topiramate treatment. The before-and-after analysis for the combined group found a reduction in mean monthly vertigo frequency (8.1–2.3 attacks per month, $P < 0.01$), mean headache frequency (5.2–2 attacks per month, $P < 0.01$) as well as vertigo severity (77.6–22.3 on a 0–100 VAS, $P < 0.01$) and headache severity (62.6–27, $P < 0.01$). No difference was found between the high- and low-dose groups for these outcome measures. However, the higher dose was associated with greater side effects, with 27% of patients on 50 mg twice daily discontinuing treatment early compared with no patients on 25 mg twice daily. Rates of side effects overall were higher with topiramate than with lamotrigine or sodium valproate, with 63% reporting paraesthesia and 47% reporting reduced appetite (which is sometimes welcomed by patients). A retrospective multiple-arm study by Dornhoffer *et al.*[58] included 13 patients who were treated with topiramate 50 mg twice daily, with variable treatment duration and follow-up. The main aim of the study was to identify patient factors influencing response to therapy; however, it also reported the change in DHI for individual treatments. In topiramate patients, mean DHI improved by 18.1 points from pre- to post-treatment, which was reported as not statistically significant; however, it was likely underpowered to detect a difference. The majority of patients also underwent vestibular rehabilitation and some patients were treated with more than one prophylactic medication; however, the authors did not report how many patients on topiramate received additional medication, nor did they report the outcomes of 'non-compliant' patients or information on side effects. Two further multiple-arm studies included small numbers of patients treated with topiramate, and similar to other medications included in these studies, self-reported measures of vertigo and headache severity were found to be improved post-treatment compared to pre-treatment.[44,45]

Similar to a number of other treatments, there have not been any studies comparing antiepileptics to placebo or another control group in VM, making it difficult to definitively attribute improvements to the active treatments.

Authors' comments

Lamotrigine and sodium valproate may reduce vertigo frequency, and topiramate may reduce severity and frequency of vertigo and headache in VM, although the studies were of low quality. Topiramate is associated with a high rate of adverse effects, particularly at doses of 50 mg twice daily and above. The use of sodium valproate and topiramate in women of childbearing age is limited by teratogenicity.

Acetazolamide

Acetazolamide is used in familial hemiplegic migraine and episodic ataxia, where its mechanism of action is uncertain,[64] but it is not a standard treatment for typical migraine. It was examined in one dedicated study and one multiple-treatment-arm study in VM. The first study was a retrospective before-and-after analysis of 50 patients prescribed acetazolamide 250 mg twice daily.[65] After treatment, there was an improvement in mean monthly vertigo frequency (3.9–1.4 attacks per month, $P < 0.01$), monthly headache frequency (5.6–2.3 attacks per month, $P < 0.01$) as well as VAS vertigo severity (5.6–2.3, $P < 0.01$) and headache severity (6.3–4.0, $P < 0.01$). However, there was a high rate of side effects (87% experienced paraesthesia) and the analysis did not include the 22% of patients who either discontinued treatment within 1 month or were lost to follow-up. In the multiple-treatment-arm study, 11 patients were allocated acetazolamide (250 mg daily); however, there was also a high discontinuation rate: only five could be analysed as two did not attend follow-up and four were non-adherent to the medication.[44]

Authors' comments

While acetazolamide has been associated with improvements in vertigo and headache measures in a before-and-after study, it is often poorly tolerated and associated with high rates of treatment discontinuation.

Tricyclics and serotonin–noradrenaline reuptake inhibitors

Despite being one of the more commonly used preventative treatments for migraine headache, there have been no dedicated studies of antidepressant medications in VM, and they have only been examined in small multiple-treatment-arm studies. Amitriptyline and other tricyclics, and venlafaxine, are thought to modulate endogenous pain mechanisms by inhibiting reuptake of serotonin and noradrenaline.[41] There were two studies involving amitriptyline, one of nortriptyline and three of venlafaxine.

A retrospective before-and-after analysis of 13 patients treated with amitriptyline 25 mg daily found post-treatment improvements in vestibular symptoms (VAS 6.4–2.6, $P = 0.001$) and headache symptoms (VAS 7.5–2.8, $P < 0.001$) after 3 months.[45] In a second study amitriptyline 10 mg daily was given for 5 weeks in 24 patients, and despite the low dose and short duration of treatment there were reductions in mean monthly vertigo frequency (17.5–5.4, no significance testing reported) and subjective vertigo and headache symptoms on a VAS.[44] Side effects were common despite the low dose of 10 mg daily: xerostomia was reported in 67% and daytime somnolence in 61%. The rate of loss to follow-up and treatment non-adherence was also high in this study (only 16 of 24 patients were analysed), although this was also seen with other treatments and may thus be better explained by methodological issues rather than amitriptyline being less well tolerated than other medications.[44]

The aforementioned study by Dornhoffer *et al.*[58] included 18 patients treated with nortriptyline 20–50 mg daily and 17 patients treated with venlafaxine 37.5–75 mg daily. As discussed earlier, treatment duration was variable, some patients were treated with additional medications or vestibular rehabilitation and only patients who were compliant with medication were analysed. Mean DHI reduced by 16.8 points in the nortriptyline patients and 26.0 points in the venlafaxine patients (both reported as not statistically significant). Venlafaxine 37.5–150 mg daily was compared with propranolol 40–160 mg daily in an unblinded RCT of 64 patients.[43] The Beck Depression Inventory (BDI) improved to a greater degree with venlafaxine ($P = 0.002$); however, there were no significant differences between the two groups for the BAI or vertigo outcome measures. A before-and-after analysis of the venlafaxine group showed improvements in mean monthly vertigo frequency (12.2–2.6, $P < 0.001$), DHI (50.9–19.9, $P < 0.001$) and subjective vertigo severity (VAS 7.9–1.8, $P < 0.01$) after 4 months, similar to the improvements seen with propranolol. In another study, 75 patients were systematically allocated 3 months of treatment with low-dose (37.5 mg daily) venlafaxine, flunarizine (10 mg daily) or sodium valproate (500 mg twice daily).[57] A before-and-after analysis of the venlafaxine group showed a reduction in mean monthly vertigo frequency (5.8–3.1, $P = 0$), VAS vertigo severity (6.0–3.8, $P = 0$) and total DHI (41.7–31.3, $P = 0.001$) after treatment. Like the previous study which found superiority of venlafaxine for depressive symptoms, the emotional domain of the DHI improved to a greater degree with venlafaxine compared to the other treatments ($P < 0.05$). Tolerability of venlafaxine was comparable to the other treatments: discontinuation rate was 13% with venlafaxine and 12% with propranolol in one study[43] and 22% of patients reported side effects (with none discontinuing treatment) in the other, which was similar to the other medications.[57] It should be noted that a withdrawal syndrome with venlafaxine can complicate its use clinically.[66]

Authors' comments

Amitriptyline and venlafaxine may reduce vertigo severity and frequency to a similar degree as other medications, although like the majority of other treatments the evidence is primarily taken from before-and-after analyses. Venlafaxine is likely to have additional benefits in VM patients with concurrent low mood.

Botulinum toxin

Botulinum toxin A can be effective in chronic migraine[67] and has recently been used in three studies of VM. A retrospective review of 22 female patients who met VM criteria and received onabotulinum toxin A (155 units to 31 sites) found marked improvements both in mean migraine disability assessment score (MIDAS, 50.9–13.2, $P < 0.001$) and DHI (59.5–8.8, $P < 0.001$) 3 months after treatment.[68] Mean VAS for vertigo also improved to a large degree (8.8–0.4, $P < 0.001$) as did VM attack frequency (10.5–0.4 attacks per month, $P < 0.001$), although the methods for determining attack frequency were not stated, nor was it clear how many attacks involved vestibular symptoms and how many involved headache. Additionally, the retrospective nature of the study and lack of comparator group mean it is highly subject to bias. Another study prospectively investigated the same dose of botulinum toxin A (formulation not stated), and 74 patients with VM were recruited, started on oral preventative medication (propranolol 20–80 mg daily, flunarizine 10 mg daily or amitriptyline 25–75 mg daily) and offered botulinum toxin.[69] All patients with VM were considered for inclusion (rather than only those refractory to treatment), and the choice of whether to give botulinum toxin or not was made by the patient. Fourteen patients were excluded due to medication intolerance or failure to attend visits and 60 patients completed the study, of whom 30 received botulinum toxin. After 3 months, while mean DHI in the botulinum toxin group reduced from 63.6 to 22.7, similar improvements were seen in the group not receiving botulinum toxin (58.2–20.5) and no significant difference was found (MD 3.2, $P = 0.466$). Mean monthly vertigo frequency reduced from 6.0 to 1.1 in the group receiving botulinum toxin and from 4.9 to 1.5 in the group not receiving botulinum toxin, and while this was said to be a statistically significant finding (MD 1.5, $P = 0.003$), the higher frequency at baseline in the botulinum toxin group makes it difficult to draw conclusions from this. Migraine disability as measured by the MIDAS score improved to a greater degree in the botulinum toxin group (MD 9.5, $P < 0.001$), consistent with the known effect of this treatment for migraine headache. No serious side effects were seen, with 20% reporting pain at injection sites.[69] Finally, in a retrospective multiple-arm study, five patients with VM and prominent headache (more than 15 headaches per month) who had failed prophylactic medication received botulinum toxin (155 units to 31 sites).[58] In these five patients, mean DHI scores were essentially unchanged from pre- to post-treatment (mean reduction of 3.6 points).

Authors' comments

Botulinum toxin is likely to be more effective for headache than vestibular symptoms in VM, with no clear benefit for vestibular

outcomes seen when given in addition to preventative medication in a non-randomized study. While a beneficial effect on vestibular symptoms is still possible, this requires further research.

Physical therapy

Vestibular rehabilitation is a form of physical therapy that includes strengthening exercises, habituation exercises, canalith repositioning manoeuvres, gait retraining and sensory re-weighting tasks. It has been used in VM and other vestibular disorders with the aim of improving symptoms and function and addressing complicating conditions like persistent postural-perceptual dizziness (PPPD) or if migraine symptoms become chronic with incomplete respite between episodes. Like most of the pharmacological treatments, the evidence for vestibular rehabilitation in VM is primarily taken from before-and-after studies. There was one unblinded quasi-RCT which aimed to compare vestibular rehabilitation with pharmacological therapy, where 60 patients were systematically allocated into three groups: vestibular rehabilitation, pharmacological therapy (mainly propranolol but full information not given) and vestibular rehabilitation/pharmacological therapy combined.[70] Vestibular rehabilitation consisted of eight home sessions conducted weekly followed by home exercises twice daily for 6 months. Twenty-two percent of participants were lost to follow-up and therefore were not included in the analysis. In a before-and-after analysis of patients receiving vestibular rehabilitation alone, monthly vertigo frequency reduced from a median of 15 to 0 attacks per month ($P < 0.001$) and monthly headache frequency reduced from a median of seven to four attacks per month ($P < 0.001$). Subjective vertigo and headache severity (measured with VAS), DHI and the Activities-specific Balance Confidence Scale (ABC) also reduced after treatment, indicating reduced disability and increased confidence. There were a large number of outcome measures and the between-group comparisons were not fully reported. Vestibular rehabilitation alone or in combination with pharmacological therapy was superior to pharmacological therapy alone at reducing vertigo attack severity and duration. In contrast, pharmacological therapy alone or in combination with vestibular rehabilitation was superior to vestibular rehabilitation alone at reducing headache frequency and severity. Vitkovic and colleagues[71] performed an uncontrolled prospective before-and-after study where 23 patients with VM and 17 patients with other causes of dizziness performed home exercises for 15 min, three times daily for at least 9 weeks, with the option to continue for up to 6 months if desired. Patients with VM were limited in their activities of daily living and those with only spontaneous vertigo were excluded. Missing data were dealt with by imputation and the amount of missing data was not stated. Over the 6 months, there was improvement in mean DHI and ABC in VM patients, with most improvement occurring by 9 weeks. There were small improvements in anxiety symptoms, although in contrast to the DHI and ABC, the majority of the improvement in anxiety occurred later (between 9 weeks and 6 months). Measures of balance and sway were also found to be better after the treatment. Both patients taking preventative medication and those not taking medication improved over the duration of the study, indicating that vestibular rehabilitation may be beneficial as additional therapy in refractory patients. Another prospective uncontrolled before-and-after study included 28 patients with VM and 223 dizzy patients with tension headache or no headache.[72] Patients underwent a 5-day hospital admission to teach exercises, which were then performed at home for 30 min, 3 times daily for 4 months and were assessed after 1 and 4 months. Significance testing was not reported separately for VM patients for a number of outcome measures, and the study used a unique 9-point scale to assess symptom frequency. In VM patients, mean vertigo frequency reduced from approximately four to six times per week to approximately once per week, and mean headache frequency reduced from approximately two to six times per week to one to three times per week. Mean DHI score, headache severity [measured with the Headache Impact Test-6 (HIT-6)] and anxiety and depression symptoms [measured with the Hospital Anxiety and Depression Scale (HADS)] also improved during the therapy. For all outcome measures the majority of the improvement occurred within the first month. A small prospective study assessed the levels of pro-inflammatory mediators in 15 patients with VM before and after a vestibular rehabilitation exercise programme, which involved head movement, strengthening and balance exercises for 20 min, three times per day for 6 weeks.[73] The study also assessed clinical outcomes and found that mean monthly vestibular migraine attacks (10.6–5.3, $P < 0.001$) and subjective dizziness intensity (9.3–7.4, $P < 0.001$) both decreased after the programme. Liu and colleagues[74] performed a prospective uncontrolled before-and-after study of 19 participants with VM, who were asked to perform head movement and balance exercises at home for 10 min, twice per day for 4 weeks. The main aim was to examine the effect of vestibular rehabilitation on functional MRI although clinical measures were also reported. The article did not report the results of five patients who did not complete the study. DHI, Hamilton Anxiety Rating Scale (HAMA) and the role physical and role emotional domains of the Short Form-36 (SF-36) quality of life measure improved after the treatment period. The Hamilton Depression Rating Scale (HAMD) improved, but this was not statistically significant ($P = 0.064$). Thirty patients with refractory VM and 30 patients with other vestibular disorders were analysed in a retrospective study where subjects underwent physiotherapist-supervised sessions involving static exercises, dynamic exercises and dynamic posturography three times weekly for 6 weeks.[75] Using a non-validated 7-point Likert scale, vertigo frequency in VM patients was approximately two to three times per week and headache frequency was approximately four to six times per week at baseline, and both of these reduced to less than once per week after the therapy (P reported as <0.05 for both). There were also marked improvements in DHI, VADL and measures of balance determined by dynamic computerized posturography. Finally, in the study by Dornhoffer *et al.*,[58] 29 patients began a tailored vestibular rehabilitation programme in addition to receiving prophylactic medication. The 20 patients who continued with the programme had a greater improvement in DHI following treatment (mean reduction of 24.5 points compared to 16.5 points for all 29 patients), although change in DHI and compliance with the programme were not significantly correlated ($P = 0.243$).

Overall, vestibular rehabilitation is consistently associated with improvement in VM, particularly for balance, degree of disability and vertigo symptoms, including in patients refractory to medical treatment.[71,72,75] The majority of improvement occurred early in therapy.[71,72] There were also overall improvements in measures of headache[70,72,75] and anxiety and depression[71,72,74] in several studies, although in our experience a subset of patients who receive vestibular rehabilitation report a worsening of headaches (and dizziness symptoms), particularly in the early stages of the therapy. Nearly all the evidence was from before-and-after analyses, noting the challenges of performing controlled studies of physical therapies. The specifics of the particular rehabilitation regimens are described in various detail in the original papers and are beyond the

scope of this review. While there are no particular adverse effects from vestibular rehabilitation, dropout rates may be high[70,74,76] as positive feedback, support and particularly motivation for unsupervised programmes may be lacking. It is thus important to ensure patients have appropriate follow-up and to institute alternative treatment if necessary.

Authors' comments

Vestibular rehabilitation is safe and may improve vertigo symptoms, level of function, headache and anxiety and depression symptoms in some patients with VM, especially where symptoms have become chronic with incomplete resolution, or there is associated PPPD. We would suggest that the patients that are most likely to benefit are those who are able to tolerate some degree of 'real-life' self and external motion (i.e. moderate rather than severe symptom load) and patients who are unable or unwilling to try preventative medications.

Lifestyle, dietary and complementary measures

Potentially avoidable triggers are commonly cited by migraineurs[77] and thus lifestyle measures are recommended by most guidelines for treatment of migraine headache. One dedicated study assessed a lifestyle intervention in 41 patients with VM who were not on preventative medication.[78] Patients were given written information, which included advice to eat regular meals, information on possible dietary triggers, tips to improve sleep and an exercise programme. Of the patients who completed the study, there were significant reductions in mean DHI (45.8–30.1, $P < 0.0001$) and the headache disability inventory (HDI) (43.1–29.6, $P < 0.0001$) at a mean follow-up of 105 days; however, this did not include the 32% of patients who were not analysed mainly due to requesting pharmacological treatment or not attending follow-up, meaning that the true effect size is likely to be lower. Patients were more compliant with avoidance of dietary triggers than the other lifestyle advice; however, improvement in sleep was most closely correlated with improvement in outcomes.

In addition, multiple studies gave dietary and lifestyle advice as co-interventions and two studies assessed the effects of such advice. A retrospective study mainly focused on lomerizine for vestibular migraine prevention also examined the role of diet.[52] All patients were initially treated with dietary advice alone, which included advice to avoid 'food such as aged cheese, processed meat and certain red wines'. If dietary change had been tried previously or was unsuccessful, lomerizine or a different medication was commenced. The article did not state how long dietary advice was trialled for before medication was started. Four of 33 patients (12%) were reported to have complete resolution of symptoms with diet alone. In a study comparing cinnarizine plus diphenhydramine plus dietary/lifestyle advice with dietary/lifestyle advice alone,[54] 6-monthly vertigo frequency reduced from a mean of 3.5 to 2.2 in the 11 patients receiving the conservative measures ($P = 0.005$). Six-monthly headache frequency reduced from a mean of 2.6 to 2.0 ($P = 0.06$). The specific dietary and lifestyle advice given was not explained in detail.

Authors' comments

While the evidence is limited, there may be a role for lifestyle intervention in VM, including regular exercise, sleep advice and avoidance of fasting and potential dietary triggers.

My patient has VM—what should I do?

The evidence from studies included in this review is of almost universally low quality, making interpretation complex; however, this does not necessarily imply lack of treatment effect. Treatment recommendations (Box 1) summarize the available evidence both in terms of efficacy but also side-effect profile. It seems prudent to highlight that, as for any condition, one should not treat 'vestibular migraine' but rather the patient, and thus an individualized approach may be necessary, considering both the clinical and demographic features, but also psychological variables that commonly coexist in this (and any other) chronic disorder. The sometimes violent and almost always disconcerting and incapacitating loss of control that is associated with unpredictable vertiginous attacks renders this latter point of particular importance. Such an individualized treatment approach that nevertheless utilizes available evidence to fit the particular person can maximize patient acceptance of treatment as well as the chance of a positive response. Examples of real-life scenarios are given in Box 2 and Box 3.

Abortive treatment

There is insufficient evidence to recommend any specific pharmacological therapy for the termination of acute vertigo attacks in VM. Neuromodulation (eTNS and VNS) may be of benefit in some patients but requires further confirmation in placebo-controlled studies. The use of so-called 'vestibular sedatives' (e.g. prochlorperazine, cyclizine, cinnarizine) is widespread across dizziness syndromes and may be of benefit in patients with VM with coexistent motion sickness or nausea,[79] although there is no specific evidence for these agents in VM. It is important to avoid taking these medications more than 10 days per month, because regular use can cause patients to become sensitized to their effects and there is also a risk of withdrawal.[80] Similarly, it is important to avoid taking analgesics or triptans more than 10 days per month due to the risk of analgesic-overuse headache.

Preventative treatment

No one pharmacological therapy has been shown to be clearly superior to another for VM prophylaxis. All before-and-after studies demonstrated clinical improvement, with no serious and usually low rates of adverse effects reported. Where studies involved multiple treatment arms, there was no clear superiority of one agent over another. The American Headache Society recommends starting preventative medication in patients with at least three to six (depending on severity) migraine headaches per month,[81] and while no such recommendations exist for VM, given the relative lack of abortive treatment options, a lower threshold may be applied, in discussion with the patient. In general, medications should be started at a low dose and slowly titrated up to response: this principle was demonstrated in the study of topiramate where higher-dose treatment with was associated with increased side effects and medication discontinuation.[63] In patients who fail a medication, we typically treat with one drug at a time to minimize adverse effects, although some authors have advocated using polytherapy.[58,82]

The main preventative treatment options include flunarizine, propranolol, tricyclics, sodium valproate, low-dose topiramate (25 mg twice daily) and venlafaxine, which have all shown benefit in before-and-after analyses in VM and are established treatments for migraine headache.

Box 1 Treatment options for management of vestibular migraine based on efficacy and side-effect profile data

All patients

Lifestyle advice—discuss sleep, exercise, stress, avoidance of fasting, potential dietary triggers, alcohol, caffeine

Abortive treatment—use less than 10 days per month

(a) Simple analgesics/NSAIDs/triptans for headache
(b) Vestibular sedatives (cyclizine, prochlorperazine, cinnarizine) for vertigo
(c) Consider prochlorperazine, cyclizine, cinnarizine, or domperidone for nausea

Preventative treatment—best efficacy evidence and lower rates of serious unwanted effects

(a) Tricyclics (amitriptyline, nortriptyline)—consider if comorbid pain or insomnia.
Start 10 mg at night and titrate up in 10 mg increments every 1–2 weeks. Usual dose range 10–150 mg at night. Lower doses are often effective for VM symptoms; higher doses (≥75 mg) may benefit patients with anxiety/depression, although in our experience patients with VM rarely tolerate this much.
(b) Propranolol—generally well-tolerated in studies. Avoid in asthma, bradycardia, hypotension, and use with caution in type 1 diabetes mellitus.
Start at 20 mg twice daily and titrate up every 1–2 weeks by 20–40 mg twice daily. Usual dose range 20–80 mg twice daily.
(c) Flunarizine—consider if comorbid insomnia. Many patients report side effects (e.g. somnolence, weight gain) but rates of discontinuation are low. Need long-term monitoring to check for parkinsonism, so use with caution in elderly.
Start at 10 mg at night (no need for dose titration) in younger patients, or 5 mg at night in older patients (>65 years).

Preventative treatment—evidence of efficacy but risk of more serious unwanted effects

(a) Topiramate—consider in obese patients. Avoid in underweight patients, women of childbearing potential (unless on reliable contraception) and those with uncontrolled low mood (risk of depressive symptoms/suicidality).
Start at 25 mg at night and slowly titrate up by 25 mg every 2 weeks as effective/tolerated. Often poorly tolerated at higher doses. Usual dose range 25–100 mg twice daily.
(b) Sodium valproate—avoid in obese patients. Contraindicated in women of childbearing potential.
Start at 200 mg twice daily and titrate up by 200–400 mg every 1–2 weeks. Usual dose range 200–1000 mg twice daily.
(c) Venlafaxine—consider if comorbid low mood. *Note*: can raise blood pressure and risk of withdrawal syndrome—essential to counsel patients to avoid sudden cessation.
Start at 37.5 mg daily and titrate up by 37.5–75 mg every 2–4 weeks. Usual dose range 37.5–225 mg daily.

Preventative treatment—limited efficacy evidence in VM—could be considered if failure of multiple other options

(a) Lamotrigine—generally well tolerated. Very slow titration needed due to risk of rash/Stevens–Johnson syndrome. Note interaction with sodium valproate.
Start at 12.5 mg daily (in patients not on sodium valproate). See British National Formulary (https://bnf.nice.org.uk/drug/lamotrigine.html) for titration instructions. Usual dose range 50–100 mg twice daily.
(b) Candesartan—safe and well-tolerated. Consider if comorbid hypertension, although caution needed with respect to renal artery stenosis. No studies in VM.
Start at 2 mg daily and titrate up by 2–4 mg every 4 weeks. Usual dose range 2–16 mg daily.
(c) Nutraceuticals (riboflavin/coenzyme Q10/magnesium)—safe and well-tolerated. May be used separately or in combination. Useful in patients desiring 'natural' treatment. No studies in VM.
Dose riboflavin 400 mg daily, coenzyme-Q10 150 mg daily, magnesium 400–600 mg daily (no need for dose titration).
(d) Botulinum toxin A—likely to be more effective for headache than vestibular symptoms. Could be considered as a last resort in very refractory patients if available, if they have prominent headache and if other treatments have failed. Not funded for vestibular migraine in the UK.

Preventative treatments currently undergoing evaluation

Calcitonin gene-related peptide (CGRP) inhibitors
Acupuncture

Vestibular rehabilitation

Consider in patients refractory or intolerant of pharmacological treatment and in patients desiring a non-pharmacological approach. Particularly useful if attacks are very frequent, concurrent persistent postural-perceptual dizziness (PPPD) or disabling avoidance behaviours. Availability and expertise may be limited in some centres so consider referring to tertiary centre.

Flunarizine 10 mg daily is the only treatment that has demonstrated benefit (for vertigo frequency and symptom severity) compared to a control group, albeit without a placebo and in a study with significant methodological flaws.[56] While not meeting criteria for inclusion in this review, a service evaluation of flunarizine use at our institution found that 90% of patients experienced symptomatic improvement, and although side effects were common (reported by 50%), most patients felt that these were outweighed by the clinical benefit.[83] In our experience flunarizine is generally well tolerated; however, we recommend that patients receive long-term

Box 2 Vestibular migraine representative case history 1

Case history:
A 54-year-old female has had pulsating headaches approximately every 1–2 months since the age of 14 years, which improve if she lies in a dark room. She has no relevant comorbidities. About 2 years ago, the headaches became longer lasting (6–24 h) and more frequent (approximately weekly). Around the same time, she started to experience a 'swaying' sensation with the majority of headaches, sometimes preceding the headache but other times starting after the headache is established and lasting around 2–3 h. During these episodes she feels unsteady and often holds on to the wall when walking. She is also having occasional episodes of the swaying sensation without headache, although she still feels better in a dark room during these. She has been under significant stress and has been sleeping poorly, often taking several hours to get off to sleep. Her GP started her on propranolol for the headaches, as she had responded to this in her 30s during a period of increased headache severity. He also started her on betahistine to treat vertigo. Despite taking the prescribed treatments for 6 months and titrating propranolol up to 80 mg twice daily, she has not improved, and the vertigo episodes have become more frequent.

Analysis and management:
This patient presents a typical history and meets the Bárány Society criteria for definite vestibular migraine. Patients with vertigo are often prescribed betahistine (an H3-agonist); however, there is no role for this in vestibular migraine. It was reasonable to trial propranolol as her migraine responded to this in the past and she has trialled a reasonable dose for a good length of time.

In this case, propranolol was weaned and stopped and amitriptyline was started, chosen due to poor sleep. She also acknowledged the stressors in her life and self-referred to counselling. The dose of amitriptyline was slowly increased to 60 mg nightly—she found 60 mg caused excessive sedation; however, she tolerated 50 mg well. Six weeks after returning to 50 mg she was reviewed and had only had one further headache, which was not associated with vertigo. She was no longer having difficulty sleeping and her sense of well-being was much improved.

Learning points:
- Choose preventative medications based on comorbidities/patient profile
- Look for and address any triggers (e.g. sleep, stress, mood)

Box 3 Vestibular migraine representative case history 2

Case history:
A 30-year-old female with a history of well-controlled asthma has had migraine headaches preceded by visual aura since age 18. These are only occasional but are severe and long-lasting (up to 48 h) and associated with vomiting and the need to be in a dark room. At age 27 she developed episodes of rotational vertigo of gradual onset, lasting hours at a time. The vertigo episodes were initially infrequent but by age 29 they were occurring 2–3 times per month. She does not have concurrent headache, hearing loss or tinnitus during the episodes, but recalls that during two of them she needed to be in a dark room and that noise from the street bothered her. She was referred to a neurologist and underwent a full neurological examination, MRI of the head, pure tone audiogram and bithermal caloric testing, which were all normal. She declined amitriptyline and was started on topiramate for probable vestibular migraine. She commenced 25 mg at night but experienced brain fog which interfered with her work, so stopped the medication. She was then started on flunarizine 5 mg at night which she found helpful—the episodes of vertigo reduced to monthly and were shorter duration. Six months later she is reviewed in clinic—she has gained 5 kg, which is affecting her self-esteem and making her feel anxious. The vertigo episodes have also become more frequent again and she says she feels worse than ever and is 'dizzy all the time'. She is noted to walk gingerly and holds onto the wall and is careful about moving her head. She is on long-term sick leave from her job and avoids seeing her friends as she is fearful of having vertigo.

Analysis and management:
This patient has episodic vertigo without headache, which requires careful evaluation. The normal examination and work-up has essentially excluded other conditions and she meets criteria for probable vestibular migraine. She initially responded to flunarizine; however, she developed weight gain and her symptoms worsened despite treatment. She has avoidant behaviour and is now markedly disabled.

She was referred for vestibular rehabilitation and began a physiotherapist-supervised programme focused on balance, conditioning and confidence. Three months later she was reviewed in clinic again—she still had episodes of vertigo every few weeks, but her gait was better and she had returned to work part-time. At her next review a further 3 months later, she had only had one further episode of vertigo and her gait had normalized. She was able to work full-time and was no longer avoiding social situations.

Learning point:
Vestibular rehabilitation is a good option for patients refractory to pharmacological therapy. It is especially useful in patients with chronic symptoms and where symptoms are impacting upon emotional and/or social well-being.

monitoring due to the risk of parkinsonism with prolonged use.[84] Propranolol is also generally well-tolerated, and while there are no randomized studies, there are a number of supportive observational studies and we have certainly found it to be useful in some patients with VM. Amitriptyline was found to be beneficial in two before-and-after studies. While the small study involving nortriptyline did not find a statistically significant reduction in DHI,[58] a number of studies not meeting criteria for inclusion in the review have reported some benefit,[85,86] and our experience is that nortriptyline is of similar effectiveness to amitriptyline and can also be used. Tricyclics may be useful in VM patients with comorbid insomnia even at low doses (10–25 mg daily); if used at higher doses they may also benefit patients with comorbid depression or anxiety, although high doses may lead to increased side effects. Sodium valproate may be effective in some patients; however, it can cause weight gain and is essentially contraindicated in women of childbearing potential, which significantly limits its use in the VM population. Topiramate, like other newer antiepileptic medications (e.g. levetiracetam and tiagabine), has been associated with a high frequency of depressive symptoms in clinical trials and may also increase the risk of self-harm or suicidal behaviour,[87] thus should be used with caution in those with low mood or a history of depression. Topiramate is also teratogenic and should be avoided in women of childbearing age unless using reliable contraception. It may, however, be a good option in obese patients, as it can cause weight loss. Venlafaxine may be a good option if low mood is a significant comorbidity; however, it carries a risk of a withdrawal syndrome and patients should be counselled appropriately. Hypertension is another recognized side effect of venlafaxine therapy that appears to be dose-dependent, but its incidence tends to be low and the effect on blood pressure relatively weak,[88,89] although a case of hypertensive encephalopathy following venlafaxine has been reported.[90] Lamotrigine is not a standard treatment for migraine and there has only been one very small study in VM,[60] thus we recommend that it is considered only in patients who have failed multiple other options. In refractory patients the angiotensin receptor blocker candesartan or nutraceuticals (riboflavin, magnesium and coenzyme-Q10 alone or in combination) can be considered, although there are no studies in VM—this is justified by the fact that these treatments are well-tolerated, low risk and have evidence for benefit in migraine headache.[91–94] The evidence for botulinum toxin to treat vestibular symptoms is currently very limited and somewhat conflicting, thus currently best suited to VM patients with prominent headache, as from the current evidence it appears to be less effective for vestibular symptoms.[69] Additionally, it is expensive and may not be widely available: in the UK, botulinum toxin is funded for chronic migraine after failure of at least three other preventative treatments; however, it is not funded for VM. A single-centre analysis of CGRP inhibitors (not included in this review due to not meeting inclusion criteria) found that 60% of patients with VM retrospectively reported improvement in vestibular symptoms.[95] While there is insufficient evidence to recommend CGRP inhibitors for VM, these may become an option in the future, and the results of a clinical trial comparing galcanezumab to placebo[96] are eagerly awaited. We do not recommend acetazolamide because it is not a standard migraine treatment and is generally poorly tolerated,[44,65] and we do not recommend metoprolol due to the lack of demonstrable benefit against a placebo.[46]

It is also important to consider non-pharmacological approaches to VM. Migraine is commonly associated with triggers including stress, fatigue and fasting[77,97] and it is our experience that similar triggers occur in VM. In addition to the evidence from other types of migraine,[98] there is now some evidence that lifestyle intervention may be beneficial in VM,[78] and advice about sleep, exercise, stress and avoidance of fasting seems appropriate regardless of whether patients are on pharmacological treatment. Some patients may also find benefit by avoiding potential dietary triggers such as caffeine, nitrates, monosodium glutamate (MSG) and artificial sweeteners.[78] Vestibular rehabilitation is beneficial at least in some patients, safe, and alone or in combination with drug treatment may be better than pharmacological treatment alone for reduction of dizziness and increasing confidence.[70] Due to lack of availability in some centres and high dropout rates it is best reserved for patients with high frequency of attacks despite optimal pharmacological therapy, associated avoidance behaviours and significant impact on social and emotional well-being.

The design of future clinical trials

There is a pressing clinical need for high-quality studies into the treatment of vestibular migraine in adults, but also in children. Such studies should ideally be double-blind, placebo-controlled RCTs with pre-published protocols, a set of validated patient-centred outcome measures and adhering to Consolidated Standards of Reporting Trials (CONSORT) guidelines. As such studies represent considerable expense, it is proposed that studies investigating the treatment of other types of migraine might be designed to include a subgroup of patients with vestibular migraine. Power calculations are imperative to prevent further studies being unable to draw conclusions due to being underpowered. We identified five ongoing studies into VM prophylaxis, which are detailed in Supplementary Material.

Current validated measures for vestibular symptoms/disability include the VSS,[99] DHI,[100] ABC,[101] VADL,[102] vestibular rehabilitation benefit questionnaire (VRBQ)[103] and SF-36.[104] Although subtle ocular motor abnormalities have been reported in up to two-thirds of patients interictally[7,14–17] and abnormal vestibular function tests in 10–20% of patients,[7,10,105] these are not reliably present in VM and are unlikely to be useful outcome measures. More recently, a 'proinflammatory signature' involving interleukin-1-beta (IL-1β), C-C motif chemokine ligand-3 (CCL3), C-C motif chemokine ligand-22 (CCL22) and C-X-C motif chemokine-1 (CXCL1) has been proposed to help differentiate VM from Ménière's disease[106]: if it could be shown that treatment of symptoms corresponds with downregulation of this inflammatory cascade this may offer another outcome measure. However, comorbidities frequently present in patients with VM have been associated with systemic inflammation, including diabetes mellitus, obesity and depression,[107–109] and another study found that VM patients did not have higher cytokine levels than healthy controls.[110] Perhaps most importantly, outcome measures should reflect as closely as possible the primary goal of treatment, in this case the resolution of patient symptoms.

Conclusions

The overall evidence base for VM treatment in adults is low quality. Nevertheless, we have provided practical treatment recommendations based on the available evidence and our experience, which should be of use to clinicians treating patients with VM. Treatments not investigated by the studies covered in this review but widely used for the treatment of migraine and headache and worthy of investigation include candesartan, greater occipital nerve block, acupuncture and CGRP inhibitors. Future work might

also consider the pathophysiology of vestibular migraine, and in particular whether the headaches and episodes of vertigo are caused by the same processes and whether different clinical or pathological subtypes of VM can be identified that might show differential responses to treatment. For example, while we would argue that vestibular rehabilitation is more likely to benefit those with chronic symptoms, studies exploring the role of vestibular rehabilitation in the early stages of VM are lacking. Finally, the substantial psychological burden associated with chronic vestibular disorders along with the putative role of stress as an attack trigger in VM demands consideration of psychological intervention combined with pharmacological strategies, although in the United Kingdom such resources are often lacking. With better understanding of the pathophysiology of vestibular migraine and well-designed clinical trials, better strategies for its treatment may emerge.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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