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OTOLOGY

Analysis of the effectiveness of the prophylaxis of vestibular migraine depending on the diagnostic category and the prescribed drug

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Abstract

Introduction Vestibular migraine (VM) consists of recurrent episodes of vestibular symptoms that are accompanied by migraine in at least 50% of the episodes. The criteria of the Bárány Society include two diagnostic categories: "actual" vestibular migraine and probable vestibular migraine. There is a wide range of drugs that can be prescribed for the prophylactic treatment of VM, but recommendations for the selection of the most appropriate drug are currently lacking.

Objective To measure the extent to which the prophylactic treatment of VM reduces vestibular symptoms, headache and the number of crises depending on the diagnostic category of the Bárány Society and the drug used for prophylaxis.

Material and methods This is a multicenter prospective study. Patients with VM who presented to any of the participating centers and who subsequently met the VM criteria were prescribed one of the following types of prophylaxis: acetazolamide, amitriptyline, flunarizine, propranolol or topiramate. Patients were called back for a follow-up visit 5 weeks later. This allowed the intensity of vestibular symptoms, headache and the number of crises before and during treatment to be compared.

Results 31 Patients met the inclusion criteria. During the treatment, all the measured variables decreased significantly. In a visual analogue scale, the intensity of vestibular symptoms decreased by 45.8 points, the intensity of headache decreased by 47.8 points and patients suffered from 15.6 less monthly crises compared to the period before the treatment. No significant between-group differences were found when patients were divided based on their diagnostic category or the choice of prophylaxis prescribed to them.

Conclusion The treatment of VM produces a reduction of symptoms and crises with no significant differences based on patients' diagnostic categories or the choice of prophylaxis prescribed to them.

Keywords Vestibular migraine · Probable vestibular migraine · Treatment · Prophylaxis

Introduction

The criteria for vestibular migraine (VM), one of the causes of episodic vestibular syndrome, have recently been described [1]. A diagnosis of VM can be made when patients are suffering from recurrent episodes of vestibular symptoms which are accompanied by migraine in at least 50% of the episodes and these symptoms are not better accounted for by another diagnosis. VM is an often underdiagnosed disorder with a lifetime prevalence of 0.98% and it has a considerable impact on patients' personal life and state of health [2]. VM has been included in the "Episodic syndromes that may be associated with migraine" Section of the appendix to the third edition of the International Classification of Headache Disorders (ICHD) [3].

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The pharmacological treatment of VM involves treatment to relieve the symptoms of specific episodes and prophylactic treatments to reduce the frequency and severity of these episodes. A Cochrane review in 2015 looked at prophylactic treatments and found that seventy different drugs could potentially be used for this purpose; however, it did not find any trials which met the inclusion criteria for a meta-analysis and it could not offer any recommendations for clinical practice [4].

Since 2011, the search for the most effective treatment for vestibular migraine has been the third research priority of the Priority Setting Partnership organized by the James Lind Alliance: Ear, Nose and Throat—Aspects of Balance [5]. To this end, several studies have compared the effectiveness of different prophylactic drugs. In 2016, a prospective, randomized and controlled clinical trial compared propranolol and venlafaxine. This study found that both drugs significantly improved the score in the Dizziness Handicap Inventory and reduced the number of vertiginous attacks, the severity of vertigo and anxiety symptoms with no significant differences between the drugs; however, venlafaxine also improved the associated depressive symptoms, whereas propranolol did not [6]. In the same year, a published retrospective series of cases which compared several drugs used in the prophylaxis of VM showed that amitriptyline, flunarizine, propranolol and topiramate significantly improved headache and vestibular symptoms, whereas nortriptyline, valproate and venlafaxine did not. No statistically significant differences between drugs were found [7]. Shortly after this, another prospective randomized and controlled clinical trial compared the effectiveness of venlafaxine, flunarizine and valproate, and this study once again showed the benefits of venlafaxine in the emotional domain and the poor performance of flunarizine in decreasing the number of vertiginous attacks and the poor performance of valproate in decreasing vertigo severity [8].

These prior studies indicate that the prophylactic treatment of VM improves the symptomatology of VM and therefore conducting placebo-controlled clinical trials is difficult to justify from an ethical standpoint. However, more comparative studies are required as the question regarding which the most effective treatment is remains unanswered at present.

Objective

The objective of this study is to measure the extent to which the prophylactic treatment of VM reduces vestibular symptoms, headache and the number of crises, using the variables of diagnostic category according to the Bárány Society and the drug used for prophylaxis.

Material and methods

Screening of potential candidates

This is a multicenter prospective study. Firstly, all patients older than 14 years who presented to any of the Otoneurology Units of the seven participating hospitals with a suspected diagnosis of VM between January 1, 2017 and December 31, 2018 and who agreed to the requirements for the clinical study were initially recruited. After that, candidates were sorted according to the criteria in Table 1 and only those who did not meet any of these exclusion criteria were selected for this study. The exclusion criteria included the previous intake of any drug used in the prophylaxis of migraine and an exhaustive list of otoneurological diseases that could mimic VM.

After that, the patients that had been selected underwent a structured anamnesis. This anamnesis covered different items related to their family history, any symptoms during

Table 1 Exclusion criteria for participation in this study

Previous intake of any drug commonly used for migraine prophylaxis, regardless of the reason for having taken it
Definite or probable Ménière's disease according to the criteria of the Bárány Society [17]
Vestibular paroxysmia according to the criteria of the Bárány Society [18]
Acute vestibular syndrome in the past suggesting vestibular neuritis
Any of the forms of benign paroxysmal positional vertigo, as defined by the criteria of the Bárány Society [12], in the last 180 days, except "probable BPPV, spontaneously resolved"
Third window syndromes (excluded by using an anamnesis which included items to rule out the Vasalva maneuver as the trigger of the vestibular symptoms)
Bilateral vestibulopathy (excluded by conducting tests of vestibular function on all patients)
Selective serotonin reuptake inhibitors (SSRI) withdrawal syndrome
Any of the following neurological focal deficits related to the vestibular crisis: impairment of the ocular motricity, facial paralysis, sudden hearing loss, dysphagia, dysphonia, impaired lingual motricity, cerebellar symptoms as dysmetria or ataxia, deficits in corporal motricity or sensitivity

their childhood, a head injury prior to the development of the symptoms, cardiovascular risk factors, alcohol and tobacco consumption, medication intake (including hormonal treatments), prior otological diseases, triggers of the crises and characteristics of the headaches and vestibular symptoms. The intensity of VM symptoms, headache and vertigo, was recorded using a visual analogue scale (VAS) numbered from 0 to 100. The frequency of crises, the characteristics of headaches and its association with other migraine symptoms (photophobia, phonophobia, nausea and visual auras) were also recorded.

Next, all of the patients were submitted to a systematic neurotological exploration that included an instrumental study of nystagmus, saccades and smooth pursuit and diagnostic positional maneuvers for benign paroxysmal positional vertigo (BPPV) (Pagnini–McClure and Dix–Hallpike tests). Patients diagnosed as having concomitant BPPV were excluded from the study.

Later, audiometry and vestibular testing (video head impulse test or a videonystagmography with caloric testing, depending on the hospital) were also performed on all of the patients. A magnetic resonance imaging (MRI) scan was carried out on all patients. The protocol for MRI included T1, T2, FLAIR and diffusion sequences for the study of the brain and use of gadolinium contrast during the study of the cerebellopontine angle. All of these tests were carried out to rule out other possible causes of episodic vestibular syndrome.

Then, all of the medical records were reviewed and only those patients whose records strictly met the criteria of "actual" vestibular migraine or "probable" vestibular migraine of the Bárány Society [1] were selected. All patients who suffered from three or more VM crises a month were considered candidates for the prescription of VM prophylaxis. An automatized algorithm for the selection of prophylactic treatment [9, 10] was used to choose the most appropriate prophylactic drug for each patient from five possible options: acetazolamide, amitriptyline, flunarizine, propranolol or topiramate. This algorithm considered over 300 variables to recommend a drug and when the drugs received the same score, it suggested the most efficient one. The variables considered can be grouped into five broad categories, which are allergies, pregnancy and lactation, concomitant diseases, alcohol intake and other medication taken by the patient. These prophylactic drugs were prescribed for a course of 5 weeks and the dosage is shown in Table 2.

Finally, patients were called back for a follow-up visit 5 weeks later. This second visit involved a structured interview that included an exhaustive list of secondary effects of all the prescribed drugs. After this interview, those who did not take the prescribed drug on 80% or more of the days were excluded from the study. The proportion of missed, non-compliant and compliant patients were compared between the groups of patients using each prophylactic drug using a χ^2 test. Diagnostic positional maneuvers were carried out and any patients who had developed BPPV during the 5-week period were excluded from the study. The intensity of headaches and vertigo was measured again using the VAS, and the number of crises that the patient had had since the beginning of treatment was recorded.

Table 2 Dosage of the prescribed drugs

Acetazolamide	250 mg/24 h in the morning
Amitriptyline	10 mg/24 h one hour before sleep
Flunarizine	5 mg/24 h one hour before sleep
Propranolol	10 mg/24 h one hour before sleep
Topiramate	25 mg/24 h in the morning with a large glass of water

The informed consent of the patient or their legal guardian was required for their inclusion in this study. Those who did not consent were excluded from the data analysis. The protocol of this research study was accepted by the ethics committee of the participating hospitals.

Analysis of data

The intensity of vestibular symptoms, the intensity of the headache and the monthly number of crises before and during treatment were compared in the statistical analysis. The Student's *t*-test for paired samples was used in the event of normally distributed data and the Wilcoxon signed-rank test in the event of non-normally distributed data. The differences in these three variables before and during treatment were then compared between the groups by sorting patients based on their diagnostic category according to the Bárány Society and on the prophylactic drug chosen for them. The choice of statistical test depended on the number of groups in question and on the distribution of the data, i.e. normal or non-normal, and the Student's *t*-test, analysis of variance, Mann–Whitney *U* test and Kruskal–Wallis *H* test were used. The *p*-value considered significant was modified using the Bonferroni correction and it was set at $0.05/11 = 0.0045$.

Results

During the inclusion period, 125 patients were identified and recruited for participation in this study. An initial screening process using the exclusion criteria meant that 29 of them had to be excluded. 19 of the remaining patients suffered from concomitant BPPV and they were also excluded. Then, the MRI scans were checked, and two patients were excluded as brain space occupying lesions were found. After that, all of the medical records were reviewed and only those patients whose records strictly met the criteria of the Bárány Society

for VM were included; therefore, another 17 patients were excluded. Lastly, seven of the remaining patients did not meet the criteria for prophylaxis and 1 did not consent to participating in this study.

50 Patients were considered in this study. However, 11 of them failed to attend the scheduled follow-up visit and 8 of them did not take the medication on over 80% of the days, and thus the final sample size was 31 patients. The secondary effects of the drugs that were experienced by the patients who attended the follow-up visit are listed in Table 3. These secondary effects affected 92.3% of patients who had a prescription and 75.0% of patients who did not comply with the treatment. Some patients mentioned that secondary effects led them to stop the treatment, but they were not significantly linked to the lack of compliance (Fisher's exact test, $p = 0.101$). No significant between-groups difference in the proportion of missed and non-compliant patients was found between the groups sorted according to the prophylactic drug prescribed to them (χ^2 test, $p = 0.284$). The data on missed and non-compliant patients is shown in Table 4.

None of the 31 remaining patients developed concomitant BPPV during the treatment. Of these patients, 17 met the criteria for "actual" vestibular migraine and 14 met the criteria for "probable" vestibular migraine. In this second group, 3 patients did not experience migraine in at least 50% of the vestibular episodes and 14 patients did not meet the ICHD migraine diagnostic criteria. Regarding the prescribed prophylaxis, 5 patients were treated with acetazolamide, 16 with amitriptyline, 1 with flunarizine, 4 with propranolol and 5 with topiramate. Figure 1 shows the selection process.

Participants had an average age of 46.8 years and the proportion of women was 71.9%. The mean and median time since the onset of symptoms were 3.5 and 1.6 years, respectively.

Table 4 Distribution of missed, non-compliant and compliant patients sorted according to the prophylactic drug prescribed to them

	Missed patients (%)	Non-compliant patients (%)	Compliant patients (%)
Acetazolamide	18.2	36.4	45.4
Amitriptyline	25.0	8.3	66.7
Flunarizine	50.0	25.0	25.0
Propranolol	0.0	0.0	100
Topiramate	14.3	14.3	71.4
Total	22.0	16.0	62.0

No significant between-group differences were found ($p = 0.284$)

The average intensity of vestibular symptoms prior to treatment was 70.7 points on the VAS, decreasing to 45.8 points after 5 weeks of treatment, giving a significant difference between the value before and the value measured 5 weeks after the beginning of the treatment (Student's *t*-test for paired samples, $p < 0.001$). The intensity of headache prior to treatment was 68.8 points on the VAS, decreasing to 47.8 points after treatment, again giving a significant difference between both values (Student's *t* test for paired samples, $p = 0.003$). Regarding the number of monthly crises, before treatment the patients reported an average of 21.4 crises per month and a median of 28 crises. This value decreased significantly during the treatment and after the treatment patients suffered from an average of 5.8 crises per month and a median of 3 crises (Wilcoxon *T* signed-rank test, $p < 0.001$). Next, patients were

Table 3 Secondary effects of the drugs that were experienced by patients

	Acetazolamide [9]	Amitriptyline [18]	Flunarizine [2]	Propranolol [4]	Topiramate [6]
Xerostomia	33.3% (3)	66.7% (12)	0% (0)	25.0% (1)	66.7% (4)
Somnolence	44.4% (4)	61.1% (11)	50.0% (1)	0% (0)	33.3% (2)
Limb paresthesia	77.8% (7)	33.3% (6)	0% (0)	25.0% (1)	66.7% (4)
Constipation	33.3% (3)	33.3% (6)	0% (0)	25.0% (1)	16.7% (1)
Weight gain (> 1 kg)	11.1% (1)	38.9% (7)	0% (0)	0% (0)	33.3% (2)
Anorexia	33.3% (3)	11.1% (2)	0% (0)	25.0% (1)	16.7% (1)
Depression	22.2% (2)	22.2% (4)	0% (0)	0% (0)	0% (0)
Shortness of breath	22.2% (2)	11.1% (2)	0% (0)	25.0% (1)	16.7% (1)
Vomiting	22.2% (2)	5.6% (1)	50.0% (1)	0% (0)	0% (0)
Diarrhea	33.3% (3)	5.6% (1)	0% (0)	0% (0)	0% (0)
Miscellanea	Fatigue (1) Headache (1) Low back pain (1) Nightmares (1) Tremor (1)	Blurred vision (1)	Low libido (1)	Hot flushes (1)	Insomnia (1)

Percentages are calculated by using the number of prescriptions as the denominator. The numbers in brackets represent the absolute number of cases

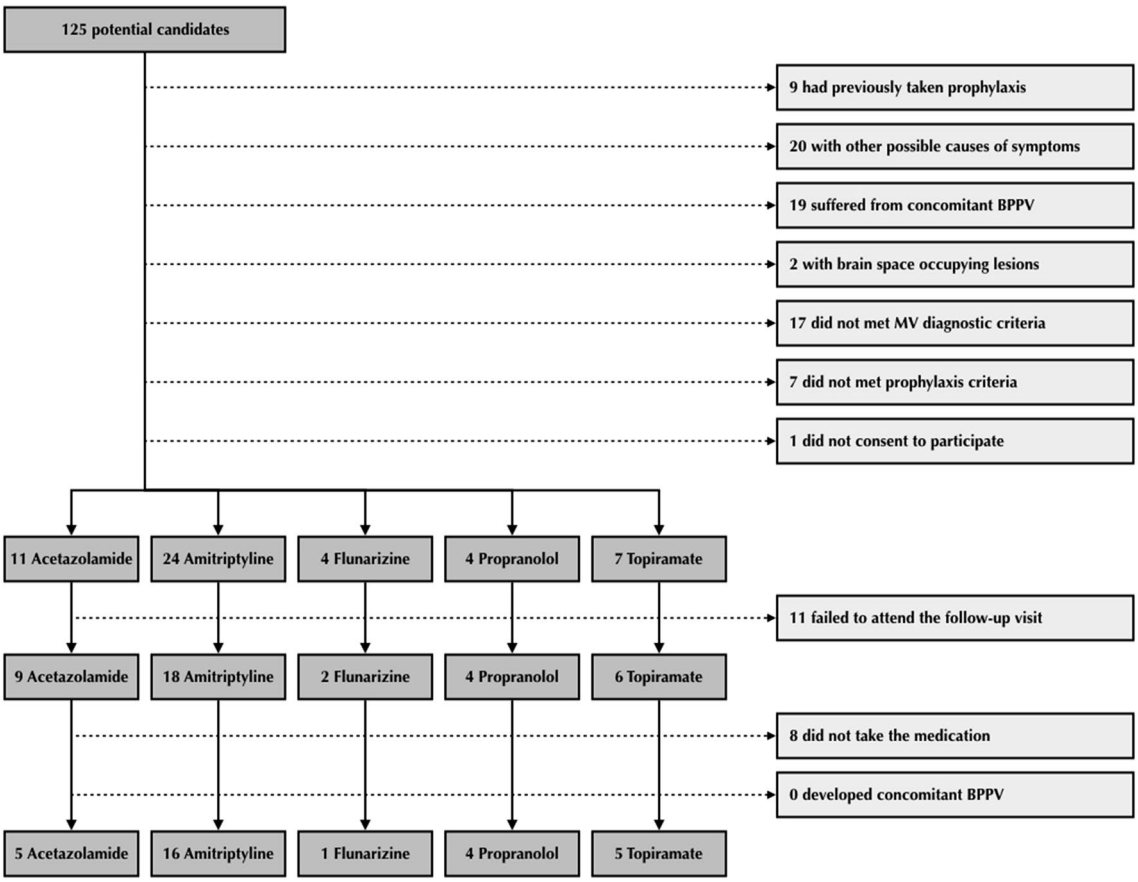

Fig. 1 Screening of potential candidates to participate in the study and their division into five study groups

sorted according to their diagnostic category: "actual" vestibular migraine or "probable" vestibular migraine. No difference was found between these groups in terms of the reduction of the intensity of vestibular symptoms (Student's t test, $p = 0.037$), of headache intensity (Student's t test, $p = 0.883$) or in the reduction of the number of crises (Mann–Whitney U test, $p = 0.951$). Finally, patients were sorted according to the drug used for prophylaxis and no differences were found between these five groups in the reduction of the intensity of the vestibular symptoms (analysis of variance, $p = 1$), of headache intensity (analysis of variance, $p = 0.800$) or in the reduction of the number of crises (Kruskal–Wallis H test, $p = 0.052$). An approximate value of the power of the comparison of the effectiveness of the prescribed drugs was retrospectively calculated using an ANOVA test. The only patient that received flunarizine was removed to do this calculation and it was assumed that all the four remaining groups had a size of 4 patients. Thereby, the power of the study was 56.6% for the reduction of the vestibular symptoms, 64.8% for the reduction of the headache and 79.0% for the reduction of the number of crises. Table 5 and Fig. 2 summarize these data.

Discussion

Effectiveness and limitations of the prophylactic treatment of VM

The main contribution of this article to the scientific literature is to quantify the improvement experienced by patients with VM after 5 weeks of prophylactic treatment. The evaluation of VM prophylactic treatment still requires validation using a randomized, placebo-controlled clinical trial; however, studies like ours, in which symptoms improve regardless of the prophylactic treatment chosen and this improvement occurs in the first 5 weeks of treatment after a mean onset of the disease 1.5 years ago, potentially raise ethical questions about conducting a trial using a placebo.

Nevertheless, the improvement seen during the treatment seems insufficient if one considers the data obtained. As shown in Table 5, patients continue to report on average six monthly VM crises despite treatment and these crises are, in most cases, accompanied by headache and vestibular symptoms. A more detailed analysis of our data indicated that only 9.7% of the patients did not notice vestibular symptoms during treatment; 12.9% did not notice headache and only

Table 5 Intensity of vestibular symptoms, headache and mean number of monthly crises, measured before and after 5 weeks of treatment

	Vestibular symptoms			Headache			Number of crises		
	Before treatment	After treatment	Difference	Before treatment	After treatment	Difference	Before treatment	After treatment	Difference
Total	70.7	45.8	24.9	68.8	47.8	21.0	21.4	5.8	15.6
Diagnostic category									
"Actual" vestibular migraine	66.9	51.9	15.0	78.3	58.1	20.2	21.4	6.1	15.3
Probable vestibular migraine	75.4	38.4	37.0	57.4	35.2	22.2	21.5	5.4	16.1
Treatment									
Acetazolamide	66.0	43.4	22.6	60.6	44.4	16.2	31.6	7.7	23.9
Amitriptyline	75.2	50.2	25.0	70.2	53.4	16.8	17.5	5.4	12.1
Flunarizine	65.0	40.0	25.0	55.0	46.2	8.8	15.0	4.7	10.3
Propranolol	68.2	43.7	24.5	74.7	33.7	41.0	27.5	1.3	26.2
Topiramate	64.4	37.0	27.4	70.6	44.6	26.0	20.4	8.7	11.7

6.4% were completely asymptomatic from the beginning of treatment. In addition, there were patients whose symptoms were not frequent enough for prophylactic treatment to be recommended. In our sample these patients accounted for 12.1% of those who met the diagnostic criteria for VM. For these two reasons, in future studies it is necessary to determine which is the most effective treatment for a single crisis of VM to relieve the symptoms of the remaining crises and those suffered by patients who do not meet the criteria for prophylaxis.

Possible biases of the results due to the exclusion process

When the study was planned, approximately 200 patients were expected to be recruited during the study period. However, the exclusion criteria established substantially reduced the final sample size. The exclusion process was carried out in five stages and each of them may have introduced a selection bias. The stages of the exclusion process were as follows:

1. Previous intake of the drugs used in the study: 9 (7.2%) of the 125 initial candidates had previously taken some form of prophylaxis for migraine. These patients were excluded to avoid a potential hindsight bias.
2. Other causes of episodic vestibular syndrome: in 20 (17.2%) of the 116 remaining candidates other causes of episodic vestibular syndrome, such as Ménière's disease or recurrent transient ischemic accidents, could not reasonably be ruled out. It is possible that in these cases the subjacent physiopathology was compatible with VM and they could have improved with a prophylactic treatment, but less typical symptoms make the diagnosis doubtful.
3. Comorbidity with BPPV: concomitant BPPV was detected in 19 (19.8%) of the 96 remaining patients. The comorbidity between VM and BPPV is well-known in the scientific literature [11]. These patients were excluded because concomitant BPPV could act as a confounding factor when the patient was asked about the intensity of their vestibular symptoms. Probable BPPV, spontaneously resolved [12] was not considered an exclusion criterion. It is difficult, even for trained neurotologists [13], to correctly diagnose probable BPPV, spontaneously resolved as it cannot be detected in any diagnostic test and both it and VM can cause episodes of positional vertigo [1, 14].
4. Brain space occupying lesions: In 2 (1.6%) of the patients, occupational brain space lesions were detected. These lesions were small cystic lesions that initially did not appear to be the cause of the patient's symptoms. However, since some brain occupying space lesions can cause intracranial hypertension and therefore headache [15] and vestibular symptoms [16], these patients were excluded.
5. VM Bárány Society criteria: in the remaining 75 patients, the diagnosis of VM seemed quite likely. However, 17 (22.7%) of these patients did not meet the diagnostic criteria for VM. In order to meet these criteria, all the requirements described by the Bárány Society [1] as well as those described by the ICHD for migraine [3] must be met. These criteria involve many conditions that subsequently increase the diagnostic specificity and thus they could be generating false negatives. The reasons for patients' failing to meet the criteria included a temporary dissociation between vestibular symptoms and a headache that did not meet the criteria to be considered a migraine, symptoms that had begun so recently that

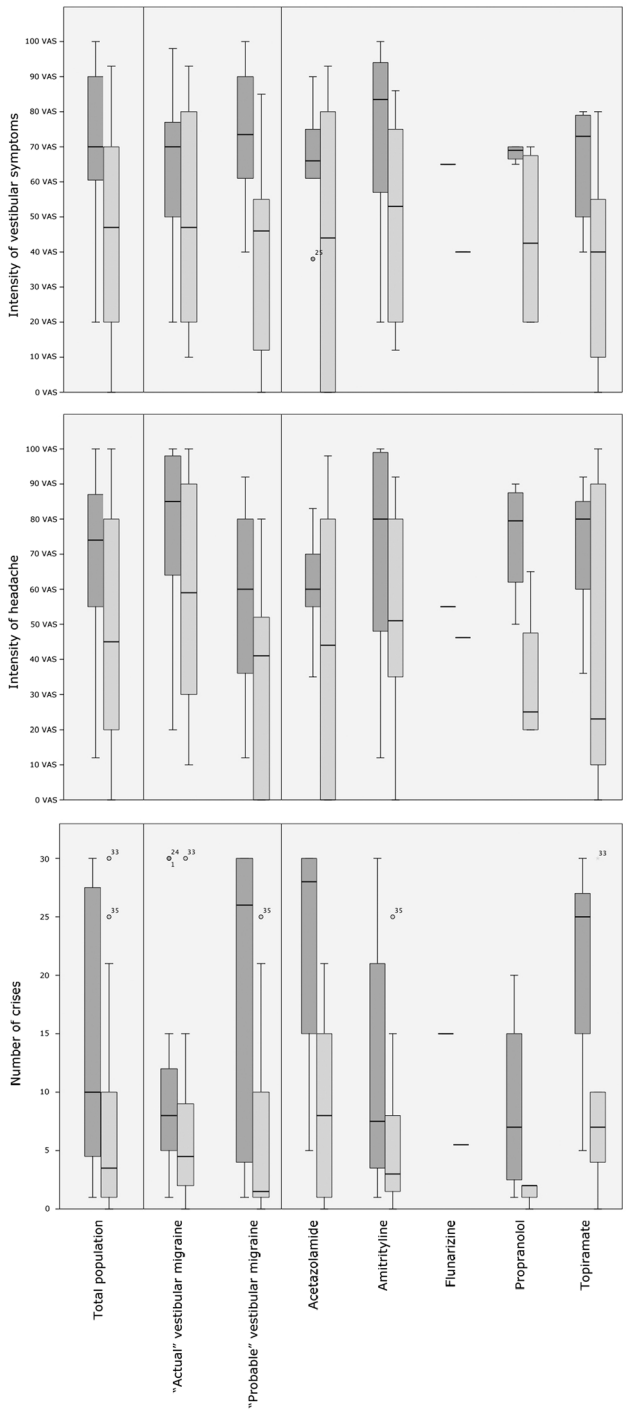

Fig. 2 Boxplots of the three variables studied. The dark gray boxplots show the pretreatment values and the light gray boxplots the posttreatment values. The total data is shown on the left and this is followed by separate data for each different diagnostic category and each of the drugs used for the prophylaxis. The intensity of vestibular symptoms and headache was measured using the VAS points. A reduction in the intensity of vestibular symptoms and headache, and a reduction in the number of crises can be seen

the patient had not yet had five episodes of vestibular symptoms, the existence of crises lasting for over 72 h or the fact that the patient reported experiencing "cephalic pressure other than pain" rather than "headache".

To summarize, if one excludes the patients who had already taken one of the prophylaxis drugs, 50.0% of the patients with suspected VM could not be given this diagnosis in the end. This is a high proportion as no better neurotological diagnosis could be made for these patients. In daily practice, it is not uncommon to encounter patients like these, and more studies are required in order to offer a treatment that is not just compassionate treatment, which is often the case at present.

Effect of missed and non-compliant patients on the results

50 Patients with VM remained after the exclusion process had been completed. However, after the treatment period, there were two types of leaks: patients who failed to attend the follow-up appointment and patients who did not follow the course of treatment correctly.

Missed patients accounted for 22.0% of the patients who were given a prescription. It is unknown why these patients decided to leave the study. Several reasons could be responsible for this leak, such as skepticism about the diagnosis, mistrust of strong antiepileptic, antidepressant or diuretic drugs, a lack of commitment to the study or the secondary effects of the drugs prescribed. As shown in Table 3, within our sample the proportion of missed patients did not differ significantly based on the drug that had been prescribed.

20.5% of the patients who went for the follow-up visit did not take at least 80% of the doses of the medication. This seems to have been caused, at least in part, by the need for a daily dose of the treatment and the secondary effects caused by the drugs prescribed. Although the secondary effects did not seem to be associated at the lack of compliance, arguably these effects do cause a lack of compliance with the treatment. As with missed patients, no significant difference was found in the lack of compliance with treatment depending on the drug prescribed.

Can "probable" vestibular migraine be considered "actual" vestibular migraine?

As previously stated, it can be very difficult for patients to meet the criteria for "actual" vestibular migraine criteria. In this sense, the criteria for "probable" vestibular migraine are laxer and easier for patients to meet. If one considers the response to treatment, patients diagnosed with "actual" vestibular migraine did not differ significantly from patients diagnosed with "probable" vestibular migraine, regardless of

whether the criterion they did not meet was that their headache could not be considered migraine or that the association of migraine with vestibular symptoms was under 50%. Therefore, from an empirical point of view, both of these can be considered to be the same as far as the response to treatment is concerned.

What is the best prophylactic drug for treating vestibular migraine?

The results of this study indicate that there is no significant difference between the drugs used for the prophylaxis of VM in terms of the improvement in vestibular symptoms, intensity of headache and the number of crises. There have been few studies thus far that have attempted to differentiate between the therapeutic profiles of these prophylactic treatments and they have found few or no differences in the improvements caused, but they have shown differences in the side effects caused [6-8]. In our clinical experience, we have had the feeling that the drug chosen for prophylactic treatment cannot be randomly chosen. 88.0% of patients that were given a prescription had comorbidities, chronic treatments or life habits that made it preferable to prescribe one drug rather than another.

One might argue that, if more patients had been recruited for this study, significant differences would have been found. However, as Table 5 shows, the mean benefit of each drug does not seem to differ in a way that is relevant to daily practice. Therefore, the results of this study indicate that at present the prophylaxis prescribed should be chosen based on the profile of each patient using the secondary effects of each drug to make an appropriate decision and using the efficiency criteria if several options are possible.

The answer to the question in the title is that the best prophylactic drug to treat vestibular migraine is the one that best fits the patient's clinical profile. Despite this, there will be patients who will have a profile with no comorbidities that will allow the prescription of several of the available drugs. According to our data, it is possible to start with any drug in these patients since the benefit obtained will be similar. Taking into account the observed high rate of side effects, we recommend using the drug with which the clinician has more experience.

The present study cannot help predict which is the best treatment for a specific patient. It is possible that a specific patient has a better response to one medication than another. Therefore, it may be necessary to change the prescribed medication if the patient's symptoms persist. In these cases, it is necessary to take into account whether the improvement or worsening caused by a change in the treatment is due to drug-dependent factors, external factors or the natural history of the disease. New studies which control the comorbidities are needed to test if any drug is superior in specific subgroups of patients with VM.

Conclusion

The prophylactic drugs used in this study to treat vestibular migraine produce a mean reduction of its symptoms (24.9 points of the vestibular symptoms and 21.0 points of the headache on a visual analogue scale) and a mean reduction of 15.6 monthly crises. No significant between-group differences in these benefits are found when patients are grouped according to the Bárány Society diagnostic category or the prophylaxis prescribed to them. Therapeutic strategies for the treatment of the remaining crises and for patients who do not meet the criteria for prophylaxis must be developed.

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Compliance with Ethical Standards

Conflict of interest None of the authors had a conflict of interest in relation with the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Lempert T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J et al (2012) Vestibular migraine: diagnostic criteria. J Vestib Res Equilib Orientat 22(4):167–172
2. Neuhauser HK, Radtke A, von Brevern M, Feldmann M, Lezius F, Ziese T et al (2006) Migrainous vertigo: prevalence and impact on quality of life. Neurology 67(6):1028–1033
3. Headache Classification Committee of the International Headache Society (IHS) (2018) The international classification of headache disorders, 3rd edition. Cephalalgia Int J Headache 38(1):1–211.
4. Maldonado Fernández M, Birdi JS, Irving GJ, Murdin L, Kivekäs I, Strupp M (2015) Pharmacological agents for the prevention of vestibular migraine. Cochrane Database Syst Rev. 21(6):CD010600.
5. Burton M, Firkins L, James LA (2011) Priority setting partnership. Ear, nose and throat (aspects of balance) top 10. https://www.jla.nihr.ac.uk/priority-setting-partnerships/ear-nose-and-throat-aspects-of-balance/top-10-priorities/. Accessed 17 Aug 2019
6. Salviz M, Yuce T, Acar H, Karatas A, Acikalin RM (2016) Propranolol and venlafaxine for vestibular migraine prophylaxis: a randomized controlled trial. The Laryngoscope 126(1):169–174

7. Salmito MC, Duarte JA, Morganti LOG, Brandão PVC, Nakao BH, Villa TR et al (2017) Prophylactic treatment of vestibular migraine. Braz J Otorhinolaryngol 83(4):404–410
8. Liu F, Ma T, Che X, Wang Q, Yu S (2017) The efficacy of venlafaxine, flunarizine, and valproic acid in the prophylaxis of vestibular migraine. Front Neurol 8:524
9. Domínguez-Durán E, Baños-López P, Martín-Castillo E, Galera-Ruiz H (2019) Inter-rater agreement in the choice of prophylactic treatment for vestibular migraine and role of an assisted algorithm for this choice. Acta Otorrinolaringol Esp
10. Domínguez-Durán E, Baños-López P, Martín-Castillo E (2019) Migratron: Algoritmo asistido para la elección de tratamiento profiláctico en la migraña vestibular. https://migratron.com/#/. Accessed 5 Jan 2019
11. Zhao PP, Xu XR, Jin ZG, Zhang Y, Li YJ (2019) Analysis of clinical features of secondary benign paroxysmal positional vertigo. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi J Clin Otorhinolaryngol Head Neck Surg 33(3):220–224
12. von Brevern M, Bertholon P, Brandt T, Fife T, Imai T, Nuti D et al (2015) Benign paroxysmal positional vertigo: diagnostic criteria. J Vestib Res Equilib Orientat 25(3–4):105–117
13. Álvarez-Morujo de Sande MG, González-Aguado R, Guerra-Jiménez G, Domènech-Vadillo E, Galera-Ruiz H, Figuerola-Massana E et al (2019) Probable benign paroxysmal positional vertigo, spontaneously resolved: incidence in medical practice, patients' characteristics and the natural course. J Otol 14(3):111–116
14. von Brevern M, Radtke A, Clarke AH, Lempert T (2004) Migrainous vertigo presenting as episodic positional vertigo. Neurology 62(3):469–472
15. Mallery RM, Friedman DI, Liu GT (2014) Headache and the pseudotumor cerebri syndrome. Curr Pain Headache Rep 18(9):446
16. Stevens SM, Rizk HG, Golnik K, Andaluz N, Samy RN, Meyer TA et al (2018) Idiopathic intracranial hypertension: contemporary review and implications for the otolaryngologist. The Laryngoscope 128(1):248–256
17. Lopez-Escamez JA, Carey J, Chung W-H, Goebel JA, Magnusson M, Mandalà M et al (2015) Diagnostic criteria for Menière's disease. J Vestib Res Equilib Orientat 25(1):1–7
18. Strupp M, Lopez-Escamez JA, Kim J-S, Straumann D, Jen JC, Carey J et al (2016) Vestibular paroxysmia: diagnostic criteria. J Vestib Res Equilib Orientat 26(5–6):409–415