Original Research

Lamotrigine Reduces the Number of Vertigo Attacks in Patients with Meniere's Disease: A Pilot Study

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Spontaneous episodes of vertigo, called vertigo attacks, are the most disabling symptom of Meniere's disease (MD). The purpose of this study was to compare the number vertigo attacks in patients with MD before and after establishing a maintenance dose of lamotrigine (Lamictal ®). A retrospective chart review was conducted on patients who were diagnosed with definite, unilateral MD, and prescribed lamotrigine for potential management of MD vertigo attacks. Patients were divided into two groups based on whether they had a history of migraine because migraine is one factor that distinguishes MD clinical subgroups. The number of vertigo attacks experienced by each patient was retrieved from clinic visit notes. The number of vertigo attacks in the 12 weeks prior to prescription of lamotrigine (Baseline) and in the first 12 weeks on a maintenance dose of lamotrigine (Maintenance) were compared via paired t-tests within the groups. Overall, thirty-three patients met criteria, of which 13 had and 20 did not have history of migraine. The number of attacks reported during Maintenance was significantly less than that reported during Baseline both for patients with (p = 0.001) and without (p = 0.0005) history of migraine. Both MD patients with and without migraine reported fewer vertigo attacks while on a maintenance dose of lamotrigine than prior to prescription of lamotrigine.

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INTRODUCTION

Meniere's disease (MD) is a disorder of the inner ear characterized by spontaneous episodes of vertigo that coincide with fluctuating sensorineural hearing loss, tinnitus, and/or fullness in the affected ear or ears.[1,2] These spontaneous episodes of vertigo, referred to as vertigo attacks, are consistently identified as being the most disabling symptom of MD,[3-5] and the severity of vertigo attacks is most strongly correlated with reductions in physical and mental quality of life for those living with the disease.[5] In turn, vertigo control is the primary outcome measure used to determine the efficacy of treatment. Treatment is recommended to progress through an algorithm of pharmacologic and surgical inventions including diuretics, betahistine, intratympanic (IT) steroids, endolymphatic sac surgery, and IT gentamicin.[6] Of these, randomized control trials demonstrate insufficient evidence to support the effectiveness of diuretics,[7,8] betahistine,[9,10] or endolymphatic sac surgery on vertigo control,[11-13] and the application of IT gentamicin is controversial because the achievement of significant vertigo control has been associated with the risk of hearing deterioration.[14-16] IT steroids, in contrast, have demonstrated significant vertigo control without negative effect on hearing in at least one randomized control trial with two-year follow-up.[17] Notably, however, the effectiveness of IT steroids on vertigo control ranges from 5-91% among all studies comparing IT steroids to placebo.[18-21] Thus, while IT steroids may offer vertigo control in some patients, they are not effective in all cases, and, as such, there remains a need for additional treatment for MD vertigo attacks.

One potential explanation for the variable success of IT steroids, and perhaps the lack of evidence to support other interventions, is that subjects are selected for clinical trials without regard for their MD clinical subgroup.[22,23] Indeed, distinct clinical subgroups exist in both the unilateral and bilateral MD populations.[22,24] These subgroups are differentiated based on the presence of delayed MD, familial cases, migraine, and autoimmune disease in unilateral MD, and, similarly, metachronic sensorineural hearing loss,

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synchronic sensorineural hearing loss, familial cases, migraine, and autoimmune disease in bilateral MD. The presence of these phenotypic subgroups suggests that there are multiple etiologies for MD. Thus, in order to clearly determine which interventions are efficacious, subjects should be carefully phenotyped in order to create uniform cohorts when selecting for and analyzing the results of clinical trials.

Homeostatic imbalance of the processes regulating the ionic concentrations of sodium, calcium, and potassium in the endolymphatic fluid has been observed in those with MD, and it has been suggested that such altered homeostasis could directly contribute to the development or maintenance of MD.[25-28] One possibility is that ionic dysregulation causes neuronal hyperexcitability and, thereby, results in the propagation of a process similar to cortical spreading depression (CSD) within the vestibular system.[26] Although the concept of spreading depression (SD) has traditionally been limited to the cortex, SD has also been observed in the retina,[29] spinal cord,[30] and cerebellum and opens the possibility of SD also occurring in other internal structures of the CNS.[31] Within the vestibular pathway, SD could be expected to result in vertigo and nausea like that characteristic of MD.[26] Notably, however, there is no demonstration of SD occurring within the vestibular system available to date. Another possibility is that ionic dysregulation of either sodium, calcium, or potassium contributes to the development of endolymphatic hydrops.[25,26,28] It has been suggested that chronically hydropic ears could be vulnerable to develop MD because they are less able to counteract the consequences of neuroinflammation that occur in innervating trigeminal nerve fibers during migraine.[27] Alternatively, we suggest that hydropic ears could damage vestibular structures so as to increase neuronal sensitivity and that hyperactivity could trigger vertigo attacks. In any case, interventions that are effective in mitigating ionic dysregulation and/or inhibiting neuronal hyperactivities should be successful at managing the symptoms of MD, including vertigo attacks.

Lamotrigine is an orally administered antiepileptic that reduces presynaptic glutamate and aspartate release through selective inhibition of voltage-gated sodium channels.[32] In addition to its efficacy to reduce seizures, lamotrigine has been shown to decrease hyperexcitability of neurons in the brain to treat patients with bipolar disorders[32,33] and to reduce the incidence of CSD-induced events including migraine aura and migraine attacks in patients with migraine with aura;[34] thus suggesting that lamotrigine has the ability to intervene in a variety of disorders associated with neuronal hyperactivity. It follows that, if MD is caused by ionic dysregulation and/or hyperexcitability of neurons in the affected ears, lamotrigine should be able to reduce symptoms of MD, including vertigo attacks. As such, the purpose of this study was to compare the number vertigo attacks in patients with definite, unilateral MD before and after establishing a maintenance dose of lamotrigine (Lamictal®). Due to the compelling evidence that migraine is a predictor of clinical subgroups in MD,[22-24] preliminary evidence of genetic dissimilarities between MD patients with and without migraine,[28] and some existing evidence of lamotrigine's effects on migraine with aura,[34] we conducted separate analyses on patients with and without a history of migraine.

METHODS

Lamotrigine

Lamotrigine (Lamictal®) was dispensed as tablets. Lamictal is an orally administered antiepileptic indicated for the management of epilepsy and as a mood stabilizer in bipolar disorder.[32] Discontinuation of Lamictal is recommended upon the first sign of rash as there is no reliable indication of which rashes will progress from benign to serious or life threatening. The incidence of rash in adults aged 18 years and older prescribed Lamictal as adjunctive therapy for epilepsy is 0.3% and as initial monotherapy or adjunctive therapy for bipolar and other mood disorders is reported as 0.08 and 0.13%, respectively, in the package insert. However, an incidence of adverse dermatologic reaction of 8.3% with no significant variance between prescription for epilepsy, bipolar disorder, or other indication has been found in a review of clinical trials.[35]

Participants

The electronic medical records of patients under the care of provider LZ from January 2011 to December 2014 at the Dizziness, Balance, and Tinnitus Center (DBTC) within Dent Neurologic Institute, an outpatient neurology clinic in Buffalo, New York, were reviewed. Data were included from patients aged 18 or older that were diagnosed with unilateral MD, reported active vertigo attacks, and prescribed lamotrigine for potential management of MD vertigo attacks. Data were excluded from patients that were diagnosed with bilateral MD, Tumarkin's crisis, or a non-vestibular neurological disorder that could account for their symptoms.

Definite MD was diagnosed in accordance with the 1995 AAO-HNS criteria which specifies that a patient must:

- experience two or more spontaneous episodes of vertigo lasting 20 minutes or longer,
- have audiometrically documented hearing loss on at least one occasion,
- experience tinnitus or aural fullness in the affected ear,
- have all other causes of these symptoms excluded.

A full vestibular battery, including a comphrehensive hearing test, tympanometry, and videonystagmopraghy, as well as either CT or MRI, was conducted on each patient in order to rule out the possibility of other vestibular disorders and confirm the presence of MD. A diagnosis of MD was considered confirmed if a patient demonstrated low and middle frequency hearing loss and other vestibular and neurologic disorders were excluded.

The criteria of 'active' MD was defined for the purpose of this study as a minimum of three vertigo attacks each lasting a minumum of 20 minutes in the 12 weeks prior to the prescription of lamotrigine. We selected a minimum of three vertigo attacks in 12 weeks as a minimum frequency to justify

the need for the prescription of a potential prophylatic medication. A minimum of 20 minutes duration is the lower threshhold established by AAO-HNS in order for an episode of vertigo to possibly be caused by MD. This minimum allows for MD vertigo to be differentiated from other sources of vertigo, such as vestibular migraine and benign recurrent vertigo, which may only have durations of 5 minutes minimum.[36]

Patients with bilateral MD and Tumarkin's crisis were excluded because both conditions may indicate advanced progression of the disease. That is, while some patients may demonstrate simultaenous sensorineural hearing loss from the onset of the disease, most patients begin with unilateral sensorineral hearing loss and develop bilateral loss over time.[37] Similarly, Tumarkin's crisis has been associated with late-stage MD and is thought to be related to increasing deterioration of the vestibular nerve. The goal of this study was to determine if lamotrigine can act as a prophylatic treatment for MD vertigo attacks and it is possible that patients with bilateral MD and Tumarkin's crisis do not represent similar pathology as patients earlier in the disease or would be responsive to prophylatic treatment given the advanced disease stage. Separate study would be necessary in these populations. Further, given the work of Frejo et al.,[22,24] bilateral and unilateral MD populations may have differing aetiologies and, thus, should not be grouped together in the same cohort.

The records of patients meeting these criteria (n = 42) were divided into two groups on the basis of whether patients had a history of migraine. The records of 13 patients with (n =13) and 20 patients without (n = 20) a history of migraine were included in the final data analysis after excluding four patients that withdrew from the study after experiencing side effects of lamotrigine and five patients that were lost to follow up. Migraine diagnosis was based on the clinical documentations in their diagnostic codes or the provider's assessment of patients' descriptions of their headaches from their medical records according to ICHD-3 diagnostic criteria.[38] Of the 13 patients with migraine, five had migraine with aura and eight had migraine without aura; none were being treated with migraine preventive treatments during the time period evaluated for this study. This study was approved by the State University of New York at Buffalo Institutional Review Board and all subjects provided informed consent.

Table 1. Minimum titration protocol and possible dose escalations and reductions. The minimum titration protocol was to escalate the dose of lamotrigine from 25mg BID to 100mg BID over 6 weeks. If a patient reported that they no longer had vertigo attacks at the end of week 6 and that the medication was well-tolerated, then 100mg BID was the patient's maintenance dose and their Maintenance phase began on the first day of taking 100mg BID. Alternatively, if a patient continued to report vertigo attacks at the end of week 6, their dose of lamotrigine was escalated to 150mg BID and they were instructed to continue at this new dose for four to six additional weeks, weeks 7-10 to 12 ($^{+}$). If at the end of the four to six additional weeks a patient on 150mg BID reported that they no longer had vertigo attacks, then 150mg BID became their maintenance dose and their Maintenance phase began on the first day of taking 150mg BID. However, if at the end of the four to six additional weeks a patient on 150 mg BID continued to report the occurrence of vertigo attacks, then their dose was escalated to 200mg BID and another follow-up occurred four to six weeks later, weeks 11-15 to 17 or 13-17 to 19 ($^{++}$). At the follow-up, it was determined whether any further escalations or reductions were necessary or if Maintenance could begin. Finally, if at the end of week 6 a patient reported that the medication was not well-tolerated and that a lower dose of lamotrigine had managed their attacks, then the patient's dose was reduced to the lowest effective dose and follow-up occurred at the end of week 10 to 12 ($^{-}$).

	Weeks	Dose	First Week of Maintenance
Minimum Titration	1-2	25mg BID	
	3-4	50mg BID	
	5-6 $^{+, ++, -}$	100mg BID	5
Dose Escalations and Reduction	$^{+}$*7-10 to 12*	*150mg BID*	*7*
	$^{++}$*11-15 to 17 or 13-17 to 19*	*200mg BID*	*11 to 13 or after additional escalations/reductions if required*
	$^{-}$*7-10 to 12*	*Lowest ED*	*7 or after if additional escalations/reductions if required*

Design

The data in a patient's chart was divided into three phases: Baseline, Titration, and Maintenance. Baseline included the 12 weeks prior to the patient's prescription of lamotrigine. In order for a patient's data to be included, a patient must have reported at least three vertigo attacks lasting 20 minutes or longer during Baseline. Titration covered the time from the initial prescription of lamotrigine to the day of the prescription of the patient's maintenance dose. In turn, Maintenance began on the day of the prescription of the patient's maintenance dose and lasted for 12 weeks following that date. The minimum protocol for Titration (**Table 1**) was to prescribe 25mg twice per day (BID) during weeks 1-2 and to escalate the dose to 50mg BID during weeks 3-4. Upon the start of week 5, the dose was escalated to 100mg BID. If the patient did not report any vertigo attacks during weeks 5-6 while on the 100mg BID dose, then the maintenance dose was 100mg and Maintenance was said to begin at the start of week 5. Conversely, if the patient reported vertigo attacks during weeks 5-6, then the dose was further escalated to 150mg BID for at least four weeks. At the conclusion of the four or more weeks, if no vertigo attacks were reported, 150mg BID was the maintenance dose and Maintenance was said to begin at the start of week 7. One patient required a further dose escalation

after 150mg BID and they were prescribed 200 mg 1qAM, 1.5 qHS. In addition to these dose escalations, it was possible for patients to experience dose reductions. Specifically, if patients did not well-tolerate the 100mg BID dose during weeks 5-6, their dose was reduced. Thus, the actual duration of Titration varied between patients on the basis of the number of dose adjustments necessary for association with a vertigo-free state and on individual tolerance of the drug. The final maintenance dosages ranged from 25mg BID to 200mg 1qAM, 1.5qHS. Duration of titration ranged from 4 to 80 weeks (20.7 ± 18.3 weeks). Throughout the study, patients attended follow-up appointments during which they were monitored for drug tolerance and reported vertigo attacks to providers. Vertigo attacks were documented in clinic notes and these notes served as the means by which the number of vertigo attacks for each patient was determined during Baseline and Maintenance.

Study Endpoints

The primary endpoint of the study was to determine whether there was a significant difference between the number of vertigo attacks lasting 20 minutes or longer at Maintenance versus Baseline separately for patients with and without a history of migraine. The secondary endpoint was to determine the degree of change in number of attacks from Baseline to Maintenance for each patient. As such, a percent difference score was calculated for each patient by subtracting the number of attacks at Baseline from the number of attacks at Maintenance, dividing by the number of attacks at Baseline, and multiplying by 100%. A percent difference score of a 50% or greater reduction was considered clinically significant.

Statistical Analysis

Analyses were performed separately on each group. Wilcoxon matched-pairs signed rank tests were performed using GraphPad Prism version 9.4.1 for Windows (GraphPad Software, San Diego, California, USA) in order to assess change in the number of vertigo attacks from Baseline to Maintenance. Significance levels were set at $p < 0.05$, two-tailed. Data are shown as means with standard deviations.

RESULTS

Patient Demographics

Eleven of the 13 patients with a history of migraine and eight of the 20 patients without a history of migraine were female. At the time of consultation, the average ages of patients with and without a history of migraine were 53 (SD = 15) and 60 (SD = 16) years, respectively.

Number of Vertigo Attacks

Lamotrigine was associated with a reduction in the number of attacks experienced by patients with and without history of migraine. That is, patients with a history of migraine reported significantly fewer attacks at Maintenance (0.62 ± 1.19) relative to Baseline (12.69 ± 10.10; $p = 0.001$; Figure 1a bars); as did patients without a history of migraine (Maintenance 1.5 ± 2.98, Baseline 9.05 ± 7.87; $p = 0.0005$; **Figure 1b** bars).

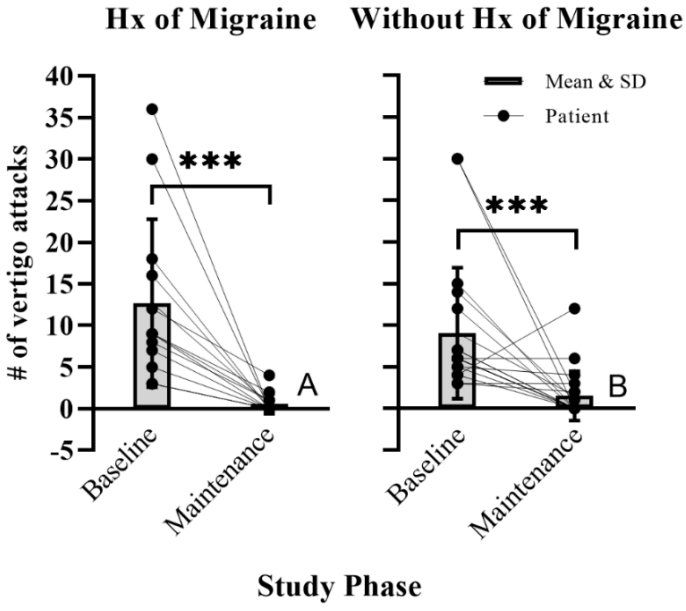

Figure 1. Lamotrigine was associated with a reduction in the number (#) of vertigo attacks from Baseline to Maintenance in patients with and without a history (Hx) of migraine. (A) The number of vertigo attacks experienced by patients with a history of migraine was reduced while on a maintenance dose of lamotrigine (Maintenance 0.62 ± 1.19) when compared to prior to prescription of lamotrigine (Baseline 12.69 ± 10.10; $p = 0.001$; *bars*). Individual patient data at Baseline and Maintenance are shown as *scatter*. (B) A similar reduction in vertigo attacks from Baseline to Maintenance was observed in patients without a history of migraine (Maintenance 1.5 ± 2.98, Baseline 9.05 ± 7.87; $p = 0.0005$; *bars*). Individual patient data at Baseline and Maintenance are shown as *scatter*.

Percent Difference Scores

A percent difference score was calculated for each patient in order to determine the degree of change from Baseline to Maintenance. Each of the 13 patients with a history of migraine demonstrated at least a 50% reduction in the number of attacks they experienced. Nine demonstrated a 100% reduction, and the rest demonstrated 89, 88, 67, and 78% reductions (**Figure 1a** scatter). Of the 20 patients without a history of migraine, 15 demonstrated at least a 50% reduction in attacks. Thirteen demonstrated a 100% reduction, two a 93% reduction, one a 200% increase, and the remaining four demonstrated reductions less than 50%, specifically 33%, 20%, 0%, and 0% (**Figure 1b** scatter).

Safety

Four patients out of the original study population of 42 (with migraine: $n = 1$; without migraine: $n = 3$) discontinued use of lamotrigine after experiencing adverse events associated with side effects of the drug. One patient experienced hallucination (final dose 25mg QID), one experienced stomachache and diarrhea (final dose 100mg BID), and two developed a rash (final doses 25mg and 150mg BID). Neither patient with rash progressed to a serious rash that required hospitalization or became life threatening. All patients experienced a resolution of their symptoms after discontinuation of the drug. Lamotrigine (Lamictal®) was well-tolerated by the remaining patients.

DISCUSSION

Current medical and surgical interventions for MD vertigo attacks do not show efficacy in all subjects. As such, there continues to exist a need for the investigation of new treatments. Here, we offer a preliminary report that lamotrigine (Lamictal®) is associated with a reduction in the number of vertigo attacks experienced by those with unilateral MD with and without migraine. We therefore propose that lamotrigine receive further study in order to evaluate fully its potential novel application as an intervention for MD.

We demonstrate here that MD patients experienced fewer vertigo attacks while on a maintenance dose of lamotrigine than prior to prescription of lamotrigine; that is, during Maintenance relative to Baseline. This finding suggests that lamotrigine may affect a mechanism responsible for the occurrence of MD vertigo attacks. Independent reviews by Sarna et al. (2020) and Teggi et al. (2021) suggest that symptoms of MD, including vertigo attacks, may be a consequence of neuronal hyperactivity affecting the processes of, or occurring within, the vestibular system. It has been suggested that this neuronal hyperactivity may either stem from ionic imbalance or result in a process similar to CSD. Evidence for the importance of ionic transportation in vestibular function and of homeostatic dysregulation of endolymphatic fluid in MD patients has been supported by both clinicohistopathological correlations and identification of genetic polymorphisms, and, thus, there appears substantial evidence to support the role of ionic imbalance in the development of hydrops and MD.[25,28] Evidence for the occurrence of SD within the vestibular system is, by contrast, currently less available but likely worth further research. For example, while CSD has traditionally been considered to occur only on the surface of the brain, it has also been demonstrated to occur in other internal structures of the CNS, including the retina,[29] spinal cord,[30] and cerebellum[31]; thus, suggesting its possibility also within the vestibular pathway. It is also possible that these processes act together, in that iconic dysregulation causes the development of endolymphatic hydrops and the distortion of the vestibular organ by hydrops could cause damage that promotes neuronal hyperexcitability. Such neuronal hyperexcitability could, in theory, cause episodic hyperactivity in the affected ear which results in vertigo attacks or make the system less able to respond to perturbations that trigger vertigo attacks.

Overall, although the precise underlying mechanism(s) are speculative, the common thread between them could suggest that MD vertigo attacks may be treated through iconic regulation and/or neuronal inhibition. The primary mechanism of lamotrigine is to selectively bind to and inhibit voltage-gated sodium channels.[32] Lamotrigine has been demonstrated to reduce epileptic seizures,[32] bipolar disorder,[33] and to potently suppress the neuronal hyperexcitability or generation of CSD in a preclinical model of migraine aura[39] and to reduce the occurrence of migraine aura and headache during migraine with aura in clinical patients.[34] Thereby, lamotrigine appears to influence a number of disorders through its ability to reduce neural activity. In turn, we propose that our data can be explained by an inhibitory effect of lamotrigine on neuronal hyperexcitability or SD affecting or occurring within the vestibular system. Alternatively, lamotrigine may counteract some of the irregularities in sodium, calcium, and potassium ion concentration in the endolymphatic system by acting as a major sodium channel blocker so as to prevent the vertigo process from being triggered.

MD is a heterogeneous disorder, and there is increasing evidence to suggest it may result from various insults, thereby increasing the likelihood that subgroup-specific treatments will be required.[22-24] Migraine was found to have a high relative importance (~ 0.8) in estimating the model for defining clinical subgroups in unilateral MD described by Frejo et al. (2017). Therefore, we separately analyzed the association between lamotrigine and vertigo attacks in unilateral MD patients with and without migraine. Of the five subgroups identified by Frejo et al. (2017), migraine was observed in all individuals belonging to Type 4 sporadic MD plus migraine, no individuals in Type 1 'classic' MD or Type 5 autoimmune MD, and in small subgroups of Type 2 delayed MD and Type 3 familial MD. In our sample, patient records suggest that our patients with migraine most likely belong to Type 4, while our patients without migraine most likely belong to Type 1, although one patient without migraine also exhibited an autoimmune disorder and thus most likely belongs to Type 5. As such, distribution of our population most likely is 58% Type 1, 39% Type 4, and >1% Type 5, which compares to the roughly 53%, 15%, and 11% distribution of these groups in the larger sample size found in Frejo et al. (2017). Our findings demonstrate that the reduction in the

occurrence of vertigo attacks from Baseline to Maintenance was similar in patients with and without a history of migraine; thus, lamotrigine may be an effective intervention for diverse MD subgroups, such as Type 4 and Type 1. Examination of the percent change in number of vertigo attacks from Baseline to Maintenance for each patient in our dataset could suggest possible differences between patients with and without migraine. That is, while all patients with migraine demonstrated a significant reduction in attacks, such a reduction was observed in 13 out of the 20 patients without migraine. This may be because our patients without migraine likely belong to Type 1, which is the largest and least well-defined subgroup.[22] Thus, it is possible that there are clinical predictors differentiating individuals belonging to Type 1 that are yet to be defined and that these differences could contribute to variability in the response to lamotrigine treatment. In turn, it is possible that, while lamotrigine could be effective for most patients with unilateral sporadic MD plus migraine, the factors contributing to lamotrigine's effectiveness for patients with classic MD without migraine could be more complex. Additional research is necessary to determine whether MD and vestibular migraine are distinct disorders or rather exist in a continuum of a single migraineous disorder.[27,40]

The most significant potential adverse effect associated with lamotrigine is rash that leads to the development of Steven-Johnson syndrome / toxic epidermal necrolysis. Review of randomized, controlled trials using lamotrigine indicate that 8.3% of patients develop a rash and that 0.04% develop Steven-Johnsons syndrome / toxic epidermal necrolysis.[35] Further, development of severe rash can be reduced through titration and most rashes appear within the first three-months of treatment.[32] The present study observed a 4.8% incidence of the development of rash (2/42 patients) and no incidence of severe or life-threatening rash when using a titration protocol. Reasons for reducing the dose of lamotrigine in this study included complaints of drowsiness and agitation. In turn, it appears that both the existing literature and the present data support that lamotrigine is generally a safe and well-tolerated medication. Thus, if proven effective in reducing the incidence of vertigo attacks in randomized control trials, lamotrigine would have the benefit of being a well-tolerated and non-invasive treatment option.

The major limitations of this study are its retrospective design and lack of placebo-control that may allow for significant placebo effects. Randomized, double-blind, placebo-controlled studies are necessary for evaluating causal effects of a drug and, thus, are needed in order to definitively demonstrate that lamotrigine can reduce MD vertigo attacks. Notably, a cross-over design would allow for within-subject observations, which may be particularly useful when managing MD patients since the frequency and severity of vertigo attacks can vary largely between patients. Nonetheless, we assert that the present data, while preliminary, does support the conduction of such randomized controlled studies, especially given the lack of science-supported alternative treatments and the possibility that lamotrigine may be effective for patients with different types of unilateral MD. Additional limitations include limited population characterization and limited duration of follow-up. Due to the retrospective nature of the study and limitations of available genetic testing, all of the data necessary for enhanced classification of patients, and, thereby, population characterization, is unavailable. As such, we can only speculate as to the unilateral MD subtypes represented in this study. Given the likelihood of variable response to treatment as a result of MD subtype, it is apparent that future studies should aim to provide a more thorough characterization of the MD patients they are representing. A prospective study carried out at multiple sites would likely allow for the best combination of characterization and representation. Further, the frequency of vertigo attacks varies both between and within patients and may be related to a number of factors including stress and weather. As such, it is most optimal to collect the longest duration of treatment or follow-up data as possible in order to capture consistent reductions in symptoms. While up to two-years of follow-up has been described in a randomized, double-blind study investigating the efficacy of IT steroid dexamethasone versus placebo to reduce symptoms of MD,[17] it may be difficult to achieve this duration since placebo-control patients may withdraw on the basis of needing treatment for ongoing MD symptoms. Thus, shorter periods of follow-up or treatment, as in the present study, may be more feasible, especially for nonsurgical, pharmaceutical interventions which negate the need for recovery time. Finally, while vertigo is a significantly limiting symptom of MD, focus should also be placed on understanding whether lamotrigine can affect the other symptoms including hearing loss, tinnitus, and aural fullness. It is possible that reducing the frequency of vertigo attacks will protect the vestibular end organ from degeneration over time and, thereby, preserve hearing and reduce the occurrence of tinnitus and aural fullness.

Although additional prospective research is necessary, this is the first study to assert the use of lamotrigine as an effective prophylactic treatment for MD vertigo. Future research into the application of lamotrigine as treatment for MD may bring about a better understanding of the etiology of the disease, as well as provide much needed relief to the patient population.

AUTHOR CONTRIBUTIONS

Conceptualization, L.Z. and D.S.; methodology, L.Z.; validation, L.Z.; formal analysis, H.P.; investigation, D.S., J.S., C.Z., K.S., and J.C.; resources, L.Z.; data curation, D.S., J.S., C.Z., K.S., and J.C.; writing—original draft preparation, H.P.; writing—review and editing, L.Z. and H.P.; visualization, H.P.; supervision, L.Z.; project administration, L.Z., D.S., and J.C.; funding acquisition, L.Z. LZ takes responsibility for the integrity of the data

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INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of The University of Buffalo (protocol code 030-4888745, approved 04/06/2018).

INFORMED CONSENT STATEMENT

Patient consent was waived due to no greater than minimal risk to patients, no direct impact on patient's rights, welfare, or clinical care, and the impracticable nature of carrying out retrospective review without waiver.

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CONFLICTS OF INTEREST

LZ holds patent US9814723B2, Compositions and Methods for Prophylaxis and Therapy for Meniere's Disease. All other authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results

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