Memantine for Episodic Migraine: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction. Migraine is a common, debilitating primary headache. Memantine is a non-competitive N-methyl D-aspartate (NMDA) antagonist that lowers neuronal excitability that could prevent migraine attacks. This study aimed to determine the efficacy and safety of memantine in patients with episodic migraine attacks using a systematic review and meta-analysis.

Methods. We searched CENTRAL, MEDLINE, Scopus, Cochrane, LILACS, ClinicalTrials.gov, HERDIN and Google Scholar for relevant studies until July 31, 2020. Prespecified screening and eligibility criteria for inclusion were applied. Included studies underwent methodological quality assessment. Study design, patient characteristics, interventions given, and relevant outcomes were extracted and synthesized.

Results. This review included five relevant articles – two randomized controlled trials (RCT) and three non-randomized studies (one retrospective records review and survey, two prospective open-label single-arm trials). There were 109 patients included in the RCTs and 197 patients reported in the non-randomized studies. Pooled data from the two RCTs showed that memantine at 10 mg/day significantly decreased the monthly number of migraine days at 12 weeks compared to placebo with a mean difference of -1.58 [95% confidence interval (CI) -1.84, -1.32]. Non-randomized studies also showed a decrease in migraine days per month with memantine (5 to 20 mg/day) after 12 weeks [95% CI]: -9.1 [-11, -7.23], -7.2 [-8.85, -5.55], and -4.9 [-6.29, -3.51]. Adverse drug events (ADE) did not differ significantly between patients treated with memantine compared to placebo.

Conclusion. Memantine may be effective and well-tolerated as prophylaxis for episodic migraine.

Keywords: memantine, NMDA antagonist, episodic migraine, systematic review, meta-analysis

INTRODUCTION

Migraine is a primary headache that is usually unilateral, throbbing, and can be associated with nausea, vomiting, and photophobia.[1,2] It has a global prevalence of 14.7%.[3] and was estimated to have caused $45.1 million-years lived with disability (YLD), which is a 51.2% increase since 1990 (as of 2016).[4]

Post-synaptic neuronal activation of N-methyl D-aspartate (NMDA) by glutaminergic transmission is well established in its involvement with mechanisms related to initiation, propagation, and chronification of migraine attacks.[5,6] Memantine is a voltage-dependent, non-competitive antagonist of the NMDA receptor that decreases glutaminergic activity, thus, possibly preventing migraine attacks.[6,7]

Memantine offers key advantages over other drugs for migraine prophylaxis: minimal and more tolerable side effects,[7] shorter time required for titration to therapeutic

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levels,[7] relatively safe use in pregnancy (safety category B),[8] and more accessible versus novel antibodies approved for the prevention of episodic migraine. Memantine may be an ideal drug option for migraine prophylaxis due to its pharmacokinetics. It has been widely used with a good safety and tolerability profile in the treatment of Alzheimer's disease, where most of the older adults taking this drug have a variety of co-morbid diseases.[9]

Most of the evidence for this drug for migraine are clinical data from observational studies, which suggest the effectivity of memantine in migraine prophylaxis. Based on the latest guidelines, memantine has only Level C (weak) evidence for the prophylaxis of migraine since, until recently, there was only one published RCT that had favorable results for memantine.[7,8] With a recently available RCT that supports memantine use, thorough evaluation of evidence is recommended.[10]

This study aims to determine the efficacy and safety of memantine in patients with episodic migraine.

METHODS

This study adhered to the Meta-analysis of Observational Studies in Epidemiology (*MOOSE*) and Preferred Reporting Items for Systematic reviews and Meta-analyses (*PRISMA*) Guidelines.[11,12]

Inclusion and exclusion criteria

We included randomized controlled trials (RCTs), prospective/retrospective cohort studies, and case series or reports. We included studies that involved patients 18 years old and above who were clinically diagnosed with episodic migraine (having less than 15 migraine days per month) according to the International Headache Society's (IHS) International Classification of Headache Disorders (ICHD-II or III).[2,13] Studies that enrolled patients who received migraine prophylaxis in the past 3 months as well as those diagnosed with chronic migraine and/or medication-overuse headache (MOH) were excluded. We considered studies that compared memantine alone or in combination with other prophylactic drugs to placebo control, regardless of drug dosage and duration of treatment. Placebo was defined as a similar-looking capsule that contained inert substance, usually sodium chloride, with no active ingredients. Any article that was not in English, dealt with the pediatric population, did not use memantine in any treatment arm, and studied other headache types were excluded.

Primary and secondary outcomes

The primary outcome for this review was headache frequency measured as the *mean number of migraine days per month*. To the determine treatment effect, the *mean difference* was computed between mean migraine days per month at a particular time of exposure to treatment and baseline.

Secondary outcomes included: 1*) intensity of headaches* measured via pain *numerical rating score (NRS)*, which is a scale from 0 (no pain) to 10 (most severe pain) and *head impact test (HIT)* that ranges from 36 to 78 with higher scores indicating an increase in severity of pain, 2) *adverse drug events*; 3) *migraine disability assessment scale (MIDAS)*, which is a 5-item tool that measures migraine-related disability and functional consequences where a higher score corresponds to more severe disability; 4) *hospital anxiety and depression scale (HADS)*, which is a 14-item questionnaire that assesses mood status on a 4-point scale wherein a higher score means a higher level of anxiety and depression; 5) Pittsburgh sleep quality index (PSQI), which is a 19-item questionnaire to assess sleep quality with higher scores indicating poorer sleep; and 6) short-form 12 (SF), which is a 12-item tool for mental and physical health-related quality of life.[14]

Search methods for identification of studies

A literature search using medical subject headings (MeSH) and free texts related to "migraine" and "memantine" were used. The following databases were systematically searched from January 2019 to May 2020: Medline (PubMed), Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov website, Scopus, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), and Health Research and Development Information Network (HERDIN) of the Philippines, and Google Scholar. The reference lists of selected studies were also searched for relevant studies.

Titles and abstracts of studies were independently screened by two reviewers according to the set criteria as mentioned. Full-text articles were obtained for relevant studies and were reviewed based on the eligibility criteria. If there were any disagreements that could not be reached through consensus, a third author (AAR) broke the tie. Included studies were then subjected to qualitative and quantitative analyses.

Data collection and analysis

Risk of bias of included studies was assessed using the Cochrane Collaboration's tool for RCTs, and the tool developed by Murad[13] for case reports/series. The latter combines eight items categorized into four domains: selection, ascertainment, causality, and reporting.[13] For this review's clinical query, questions on selection, ascertainment, and follow-up were most important to determine the risk of bias.

We extracted year of publication, study design, population size and baseline characteristics, dose and titration rate of memantine, duration of treatment, follow-up, number of migraine days, the intensity of headaches, measures for depression, cognitive performance, quality of life, withdrawals, and adverse drug events from each included study.

For continuous outcomes, we used mean differences (MD) with [95% confidence interval, CI] as a measure of treatment effect. For dichotomous outcomes, risk ratios (RR) with 95% CI were used. Data were synthesized using the Review Manager (RevMan) 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We pooled continuous outcomes using the inverse-variance method and dichotomous outcomes using the Mantel-Haenszel method. Meta-analysis was performed using the fixed-effects model. For continuous outcomes, a statistically significant difference between the intervention and control groups was noted if the 95% CI of the mean difference (MD) did not include the number 0. For dichotomous outcomes, statistical significance was detected if 95% of the RR did not include the number 1. Statistical heterogeneity was measured using the I^2 statistic, with values 0 to 40% indicating unimportant heterogeneity

RESULTS

Search results

After screening 683 records, we retrieved full-text articles for 7 studies. Two studies were excluded since they were review articles. Five studies fulfilled the inclusion criteria (Figure 1). The two randomized controlled trials were analyzed for meta-analysis.

Description of Studies

All five included studies were published in peer-reviewed journals – 3 in international journals (Charles 2007;[15] Bigal 2008;[6] Noruzzadeh 2015[7]), one local journal in Iran (Assarzadegan 2017),[16] and one local journal in India (Shanmugam 2019).[10] Details of patient characteristics and methodology used are shown in Table 1.

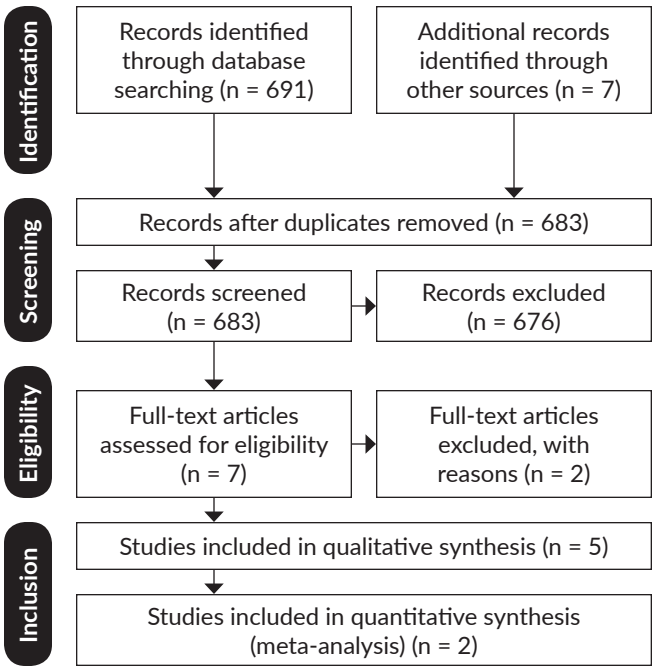

Figure 1. PRISMA study flow diagram.

Two were randomized controlled trials, two were prospective non-randomized open-label single-arm trials, and 1 was a retrospective case series. All studies based the diagnosis of migraine according to the ICDH-II. A total of 317 patients were included – 120 patients randomized for the two RCTs (30 patients in the memantine arm and 30 patients in the placebo arm, per study) and 197 for the observational studies.

There was a predominance of female participants (female-to-male ratio of 3.13:1). Age of participants ranged from 27 to 57 years. Dosing of memantine ranged from 5 mg/day to 20 mg/day depending on patient tolerance and satisfaction with pain control. Only the randomized trials used a pre-determined dose of 10 mg/day.

The main outcome for all studies focused on the number of migraine days per month from baseline to 12 weeks follow-up. For headache severity, the studies of Assarzadegan 2017 and Noruzzadeh 2015 used pain NRS, while the study of Bigal 2008 used HIT.

RCTs

Both RCTs limited their inclusion criteria to episodic migraines but Noruzzadeh 2015 included only migraine with aura, while Shanmugam 2019 included all patients classified with migraine under the ICHD guidelines.

Noruzzadeh 2015 had stricter exclusion criteria that did not consider patients who had medication overuse headaches, use of antipsychotics or antidepressants in the past three months, a recent history of alcohol or drug abuse, allergy to memantine, treatment-resistant migraine, pain disorder, severe psychiatric illness, severe infection, malignancy, low survival chance, severe cardiovascular disease, neurodegenerative disorders, pregnancy and lactation, and sexually active women. In comparison, Shanmugam 2019 excluded patients with headaches that did not respond to more than two migraine preventive medications, pregnant/breastfeeding women, medication overuse headaches, severe medical illness, renal insufficiency, hepatic problems, and hypersensitivity.

For the study of Noruzzadeh 2015, two were lost to follow-up and three discontinued intervention in the memantine arm, while three discontinued in the placebo arm. As for Shanmugam 2019, 2 were lost to follow-up in the intervention arm and 1 lost to follow-up in the placebo arm.

The two RCTs compared memantine at a fixed dose of 10 mg/day versus placebo control. Each study randomized 60 patients into 30 patients to the memantine arm and 30 patients to the placebo arm.

Both studies looked into migraine days per month starting with a baseline measurement with Shanmugam 2019 having a longer baseline phase of 3 months versus one month for Noruzzadeh 2015. Shanmugam 2019 had more frequent data point gathering set at every 4 weeks for a longer

follow-up of 24 weeks compared to the Noruzzadeh 2015, which only looked at migraine days per month at baseline and after 12 weeks.

Non-randomized studies

Charles, et al. conducted a medical records review and survey via mail involving 71 chronic migraine patients on memantine (doses at 5mg, 10mg, 15mg, and 20mg depending on patient's self- assessment of pain control). Fifty four finished the study and 67% reported a greater than 50% reduction in pain numerical scale from baseline after a 15-month period.

Bigal, et al. was a single-arm trial that recruited 38 patients with chronic migraine and gave memantine ranging from 10mg to 20mg, depending on tolerability. Of the 23 patients who completed the study, there was significant reduction of migraine days from 7.8 to 3.2 after 3 months (p<0.01).

Assarzadegan 2017 was a single-arm trial that included 127 chronic migraine patients with a 30-day observation period before beginning memantine 5mg/day, increased by 5 mg/week up to 20mg/day with no comparator. One hundred two patients completed the study and had significant reduction of migraine days from 6.9 to 3.6 after 3 months (p<0.001).

Methodological quality assessment

The two RCTs had low risk for selection, performance, detection, attrition, and reporting bias indicating an excellent level of methodological quality (Figure 2).

All three non-randomized studies had no comparators, thus alternative explanations for the noted effects could not be fully verified. There was also no challenge/re-challenge done in all studies. As for the dose-response effect, the authors graded this to be "unclear" since the maximum dose was determined by the dose at which patients were satisfied with pain control and no adverse effects were present. The remaining questions were satisfied by all three studies. Therefore, all non-randomized studies satisfactorily addressed the necessary aspects for good methodological quality (Table 2).

Effects of the intervention

Details of the results for the primary and secondary outcomes from included studies are in Table 3.

Migraine days

Two RCTs were combined in a meta-analysis for the 12-week timepoint (Norruzadeh 2015; Shanmugam 2019) (Figure 3). There was a statistically significant reduction of about 1.6 migraine days in a month at 12 weeks with memantine (10 mg/day) versus placebo (MD, -1.58, 95% CI, -1.84, -1.32).

For the three other non-randomized studies, migraine days decreased from baseline with a mean difference (95% CI) of -9.1 [-11, -7.23] (Charles 2007), -7.2 [-8.85, -5.5] (p<0.01) (Bigal 2008), and -4.9 [-6.29, -3.51] (p<0.001) (Assarzadegan 2017).

Figure 2. Risk of bias summary using the Cochrane Collaboration's Tool for RCTs.

Secondary outcomes

Based on individual studies, there was significant decrease in disability (MIDAS) from baseline, headache severity, number of days with severe pain, number of days wherein rescue medication was used, number of migraine attacks per month, number of days absent from work, number of acute pain medications used per episode, HADS for anxiety and depression, and PSQI, with an increase in the SF-12 score (mental and physical components), (Table 4).

Charles 2007 reported that patients who took memantine had (1) decreased headache severity, (2) reduced amount of medication taken, (3) improved level of function, and (4) 67% of patients had 50% reduction in monthly headaches.

There were no significant differences in adverse drug events (ADEs) based on pooled RRs from two RCTs (Figure 4). Charles 2007 reported two patients with agitation, and one patient each with a rash, cognitive dysfunction, and extremity pain. Bigal 2008 reported seven patients with somnolence, three each with anxiety, asthenia, and weight gain, two each with depression and emotional instability, one each with constipation, vertigo, and imbalance.

Table 1. Patient characteristics and methods used in included studies

Study	Design/Setting	Inclusion	Population (n=317)			Methods	
			Size	Sex (F:M)	Age (Mean)	Treatment (Memantine)	Additional Medication
Noruzzadeh 2015	Randomized, placebo-controlled, parallel-group trial	ICHD-II diagnosis of episodic migraine specifically without aura	30	3.28:1	34.8	1 month baseline observation 10 mg/day for 12 weeks	Excluded patients who received migraine prophylaxis in the past 3 months Acute pain medication was allowed
Shanmugam 2019	Randomized, double-blind, placebo-controlled parallel-group trial at a tertiary care hospital in India	ICHD-II diagnosis of episodic migraine	30	2:1	30	3 month baseline phase 10 mg/day for 24 weeks	Preventive medication was discontinued and only allowed 1 rescue medication
Charles 2007	Retrospective chart review and survey	ICHD-II diagnosis of episodic migraine	60	4.45:1	49	Initial 5 mg/ day then increased by 5 mg/week up to 20 mg/day depending on lowest dose with satisfaction in pain control 1 on 5 mg, 7 on 10 mg, 1 on 15 mg, 45 on 20 mg]	All patients had previous multiple preventive medication
Bigal 2008	Non-randomized, prospective, open-label, single-arm trial in a tertiary hospital from 2006–7	ICHD-II diagnosis of episodic migraine including refractory migraine (episodic migraine with failure to at least one preventive medication)	28	3:1	43.5	1 month baseline observation Initial 10 mg/day (19 patients, 67.85%) then after 1 month of no side effects and satisfactory pain control, dose was increased to 20 mg/day (9 patients, 32.1%) for 3 months	42.8% used one preventive drug 51.8% used 2 preventive drugs
Assarzadegan 2017	Non-randomized, prospective, open-label, single-arm trial at Hossein Hospital from 2011–2013	ICHD-II diagnosis of episodic migraine including refractory migraine (episodic migraine with failure to at least one preventive medication)	109	3.42:1	40	1 month baseline observation Initial 5 mg/day, then additional 5 mg every 2 weeks if no side effects and inadequate pain control up to total of 20 mg/day for 3 months	40.4% used one preventive drug 59.6% used 2 or more preventive drugs

ICHD, The International Classification of Headache Disorders

Table 2. Risk of bias assessment for included case reports and case series studies

Domains	Leading explanatory questions	Assarzadegan 2017	Bigal 2008	Charles 2007
Selection	1. Does/Do the patient(s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been presented?	Clear selection method	Clear selection method	Clear selection method
Ascertainment	2. Was the exposure adequately ascertained?	Yes	Yes	Yes
	3. Was the outcome adequately ascertained?	Yes	Yes	Yes
Causality	4. Were other alternative causes that may explain the observation ruled out?	No	No	No
	5. Was there a challenge/re-challenge phenomenon?	No	No	No
	6. Was there a dose-response effect?	Unclear	Unclear	Unclear
	7. Was follow-up long enough for outcomes to occur?	Yes	Yes	Yes
Reporting	8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences to their own practice?	Yes	Yes	Yes

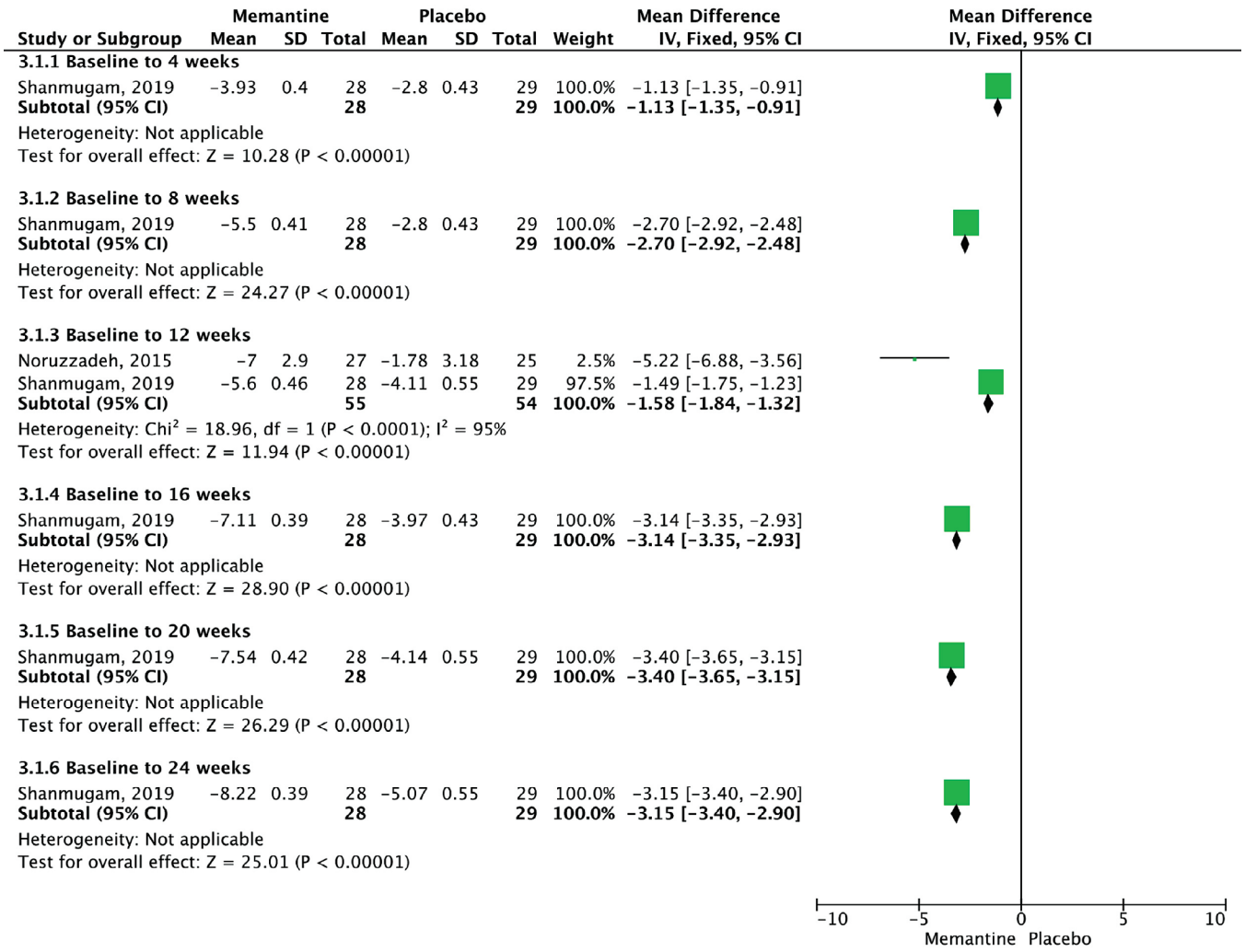

Figure 3. Forest plot: Memantine versus placebo (Headache frequency in a month from baseline to various timepoints).

Table 3. Summary of main results of included studies

Study	Monthly Migraine Days Mean Difference [95% CI]	MIDAS Mean Difference [95% CI]	Headache Severity Mean Difference [95% CI]
Noruzzadeh 2015	-7.0 [-7.73, -6.27]	-10.5 [-12.2, -8.79]	-3 [-3.43, -2.57]
Shanmugam 2019	-5.61 [-5.73, -5.49]	ND	ND
Charles 2007	-9.1 [-11, -7.23]	ND	ND
Bigal 2008	-7.2 [-8.85, -5.55]	-20.7 [-28.1, -13.3]	-17.2 [-23.6, -10.8]
Assarzadegan 2017	-4.9 [-6.29, -3.51]	ND	-3.3 [-3.59,-3.01]

MIDAS, Migraine disability assessment scale; CI, Confidence interval; ND, No data

Table 4. Summary of results for secondary outcomes of included studies

Outcome	Study	Mean Difference [95% CI]
Number of days with severe pain	1 single-arm trial (Bigal 2008)	-4.5 -5.61, -3.39]
Number of days wherein rescue medication was used	1 RCT (Shanmugam 2019)	-6.36 [-6.51, -6.21]
Number of migraine attacks per month	1 RCT (Noruzzadeh 2015)	-3.5 [-4.14, -2.86]
Number of days absent from work		-1.2 [-1.63, -0.77]
Number of acute pain medications used per episode		-1 [-1.51, -0.49]
SF-12 score (mental component)		1.1 [-1.62, 3.82]
SF-12 score (physical component)		1.9 [0.15, 3.65]
HADS (anxiety)		-1.5 [-2.63, -0.37]
HADS (depression)		-1.3 [-2.39, -0.21]
PSQI		-1.2 [-2.12, -0.28]

CI, Confidence interval; SF-12, Short form-12; HADS, Hospital anxiety and depression scale; PSQI, Pittsburgh sleep quality index

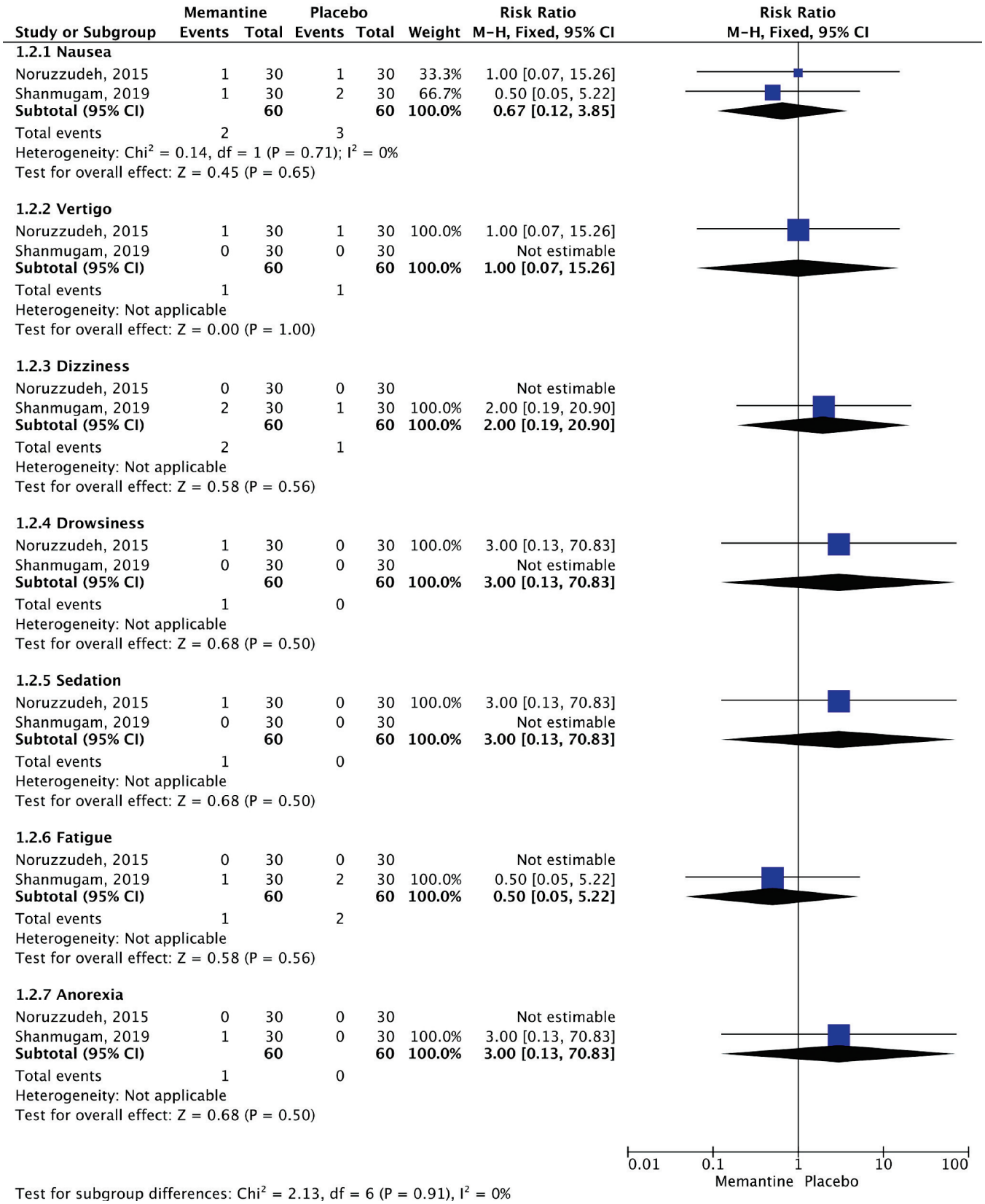

Figure 4. Forest plot: Memantine versus placebo (Adverse drug events).

DISCUSSION

Efficacy analysis based on pooled number of migraine days showed an statistically significant decrease of 1.58 migraine days per month (95% CI, -1.84, -1.32) compared to baseline at 12-week follow-up (2 RCTs, N=120; Noruzzadeh 2015; Shanmugam 2019). Qualitative reporting of three non-randomized studies also showed that patients given memantine had a statistically significant decrease of 3.51 to 11 migraine days per month after 12-weeks compared to baseline. In terms of safety, a quantitative analysis of ADEs demonstrated no significant difference between memantine and placebo. These data suggest that memantine may be an effective and safe prophylactic drug for episodic migraine.

Memantine was not included in the recommendations of the 2012 AAN guidelines since no RCTs have been published at that time.[14] Compared to Class A recommendation of topiramate (4 Class I studies, multiple Class II studies, and 1 negative Class II studies), valproic acid (multiple Class I studies), and propranolol (1 Class I study), the resulting 1.58 reduction in migraine days from two weakly powered RCTs using memantine is still not convincing and would probably need more clinical trials especially head-to-head studies.

In terms of pricing, based on the Philippine Monthly Index Medical Specialties (MIMS), memantine 10 mg (30 pieces at 900 – 1,500 Php[17] or 18 – 30 USD) is the next most affordable to valproic acid 250 to 500 mg (30 pieces at 600 Php or 12 USD) compared to topiramate 25 to 100 mg (30 pieces at 4,000 Php or 80 USD) and propranolol 40 mg (10 to 30 pieces at 3,000 Php or 60 USD).[17]

According to the Global Burden of Disease Study last 2010, migraine ranked third in prevalence worldwide as well as the third-highest cause of disability across both sexes under the age of 50.[2] According to the American Association of Neurology (AAN) last 2012, around 38% of migraineurs need preventive therapy, but only 3%-13% avail of preventive medication.[18] Prevention of migraine can lead to significant improvement in health-related quality of life.

In one recent review by Rau and Dodick 2008,[14] which incorporated guidelines from the American Association of Neurology (AAN), American Headache Society (AHS), and Canadian Headache Society (CHS), they listed alpha-adrenergic agonists, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and serotonin antagonists as preventive migraine agents. Targeted therapy via monoclonal antibodies has also been used for migraine treatment. In 2018, erenumab, fremanezumab, and galcanezumab were approved for prophylaxis for episodic migraine. However, for most of these drugs, intolerable side effects and cost are the common barriers for patient compliance.

Most experiences with memantine for migraine were clinical data from observational studies, which all showed positive results suggesting the effectivity of memantine in migraine prophylaxis. Based on the latest guidelines, memantine has only Level C (weak) evidence for the prophylaxis of migraine since until recently, there was only one published RCT that had favorable results for memantine.[7,8] With recently available RCT that supports memantine use, thorough evaluation of evidence is recommended.[10]

The study design inclusion criterion for this review was deliberately expanded to include non-randomized studies to generate a more comprehensive analysis due to the paucity of currently published RCTs. Episodic rather than chronic migraine was prioritized since most drugs for migraine prophylaxis would initially be evaluated for acute attacks prior to proceeding to chronic migraineurs. The frequency of headaches expressed as migraine days in a month was the primary outcome measured. Since the prevention of attacks is the primary concern, the duration of each attack would be less appropriate to analyze as this is more of a measure migraine attack termination. Based on these parameters, evidence gathered from this review is applicable to patients experiencing migraine attacks of less than 15 migraine days in a month.

The risk of bias was considered low for the two RCTs. All included non-randomized studies adhered to a common reference for migraine diagnosis, provided a reproducible methodology, and presented the necessary data to evaluate the efficacy of memantine for migraine prophylaxis – showing good methodological quality.

There are significant observations identified in this review regarding the study populations, length of follow up, use of preventive and rescue medications, clinical significance and relevance to patient quality of life of reported outcomes.

There was significant clinical heterogeneity in terms of the populations enrolled in the RCTs. No subgroup distinction between migraine with and without aura was made. Although both migraine types are usually treated similarly, it has been suggested that response to treatment may be different for migraine sub-types due to their distinct pathophysiology.[19] Stricter inclusion criteria that will ensure homogeneity will thus benefit future studies to determine if the subgroup analysis of pure migraineurs with and without aura will have an effect. There were differences in doses used in the non-randomized studies. The dose of 10 mg/day used in RCTs was based on previous observational studies that determined this as the maximal dose wherein patients had satisfactory pain control with no adverse drug effects. Memantine dosing can go as high as 20 mg/day; thus, it would be judicious to explore the effects of an increased dose for memantine in future migraine prophylaxis studies.

Data extrapolated from the small sample size of both RCTs may inherently cause the imprecision of measured outcomes. Larger sample size should be used in future RCTs to generate a stronger level of evidence.

Although all studies considered a similar time point for follow up, an extended duration of drug exposure can be

explored as was done in Shanmugam 2019 especially since data from this study suggested that a significant difference in headache frequency was only evident after 16 weeks.

The use of other preventive and rescue medication was not fully controlled in all included studies. For succeeding studies, it would be advantageous to examine patients with no previous exposure to any prophylactic medication to remove carry-over effects.

Allowing acute rescue drugs in the clinical trials is a common issue, which may obscure data in studies dealing with a placebo comparator since the decrease in migraine days may be from the rescue drugs. However, especially in trials that deal with pain, it is unethical to withhold any treatment to patients experiencing acute pain; hence this is an inherent bias in any drug trial dealing with pain relief. Additionally, in both RCTs, the chronic migraine patients were known to be taking prior rescue drugs and were subjected to a 30-day drug free observation period for baseline data. Medication overuse was also part of their exclusion criteria. Therefore, we can assume that these patients have already been taking their usual rescue drugs and still had more than 15 migraine days in a month. Allowing rescue doses in conjunction with the trial drug of memantine can therefore be justified and the treatment effect seen in the studies can be considered valid.

It is important to determine if the positive treatment effects that were measured in the included studies were actually clinically significant. It has been shown that placebo effect for migraine studies can reach up to 30%. For this reason, the non-randomized and non-placebo studies showed high reduction rates in migraine days.[20] Thus, it should be noted a major limitation in the interpretation of our results is that fact that studies included in our analysis may be highly influenced by placebo effect. Disability measures such as MIDAS may help define more meaningful results that could translate to clinically significant outcomes.[14] Not all included studies reported quality of life outcomes; thus, it is highly recommended to expand the analysis to include these measures to determine if statistically significant results on reduction of migraine days translate to patient-important outcomes.

Level of Evidence

This review provides a weak level of evidence for the efficacy of memantine for the prevention of episodic migraine based on the pooled data from two RCTs with low risk of bias but with relatively small sample size. The point estimates with its confidence intervals of the treatment effects for efficacy outcomes measured did not cross the statistical threshold to dissuade from the use of memantine.

CONCLUSION

Memantine is beneficial and well tolerated in migraine prophylaxis. Memantine resulted in a significant decrease in migraine days per month and insignificant occurrence of adverse events compared to placebo. We recommend further high quality RCTs with larger sample size and determination of dose-response effect of memantine. Effects of memantine on clinically significant outcome measures for patients with episodic migraine should be explored. Head-on comparison of memantine with other active drugs may be necessary to determine the place in therapy of memantine among the available prophylactic drugs for migraine.

Statement of Authorship

Mark Willy L. Mondia, MD and Adrian I. Espiritu, MD – Conceptualization, data curation, formal analysis, interpretation of data, writing original draft, writing-review, and editing.

Martha L. Bolaños, MD and Artemio A. Roxas, Jr., MD, Msc – Interpretation of data, writing review, and editing.

All authors approved the final version of manuscript submitted.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

No funding support.

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