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Efficacy and safety of eptinezumab as migraine preventive therapy: A systematic review and meta-analysis

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ABSTRACT

Migraine is one of the most common types of primary headaches worldwide (about 20%) besides a tension-type headache. Several types of migraine medications have been introduced and used. Drugs acting on calcitonin gene-related protein have been developed recently and have shown positive results. We conducted an updated meta-analysis to determine the efficacy and safety of eptinezumab as a migraine preventive therapy. Eight studies were found eligible and included in this review. We found that the use of eptinezumab (100 mg and 300 mg) for 24 weeks reduced the mean monthly migraine days (−1.89 *vs*. −1.52). The use of eptinezumab 100 mg also reduced the mean Headache Impact Test-6 score for 12 weeks significantly [−7.36 (95% CI −8.25 to −6.48), $p < 0.00001$]. The summarized results of the incidence of any events at each dose showed no significant difference ($p = 0.07$), and nasopharyngitis was the most frequently reported adverse event ($n = 245$). In conclusion, eptinezumab is safe and effective and can be considered as a migraine preventive therapy.

INTRODUCTION

Migraine is one of the most common types of primary headaches worldwide (about 20%) besides a tension-type headache. The lack of attention to migraine could lead to uncontrolled or chronic migraine. Uncontrolled migraine impacts the quality of life and has long-term unwanted effects, such as strokes (Stovner *et al*., 2018) (Øie *et al*., 2020). Moderate to severe migraine attacks could interfere with daily activities. Thus, productive time is reduced, and this potentially reduces the quality of life. Therefore, migraine needs to be treated adequately to reduce disability due to migraine attacks (Manack *et al*., 2011).

Several migraine medications have been introduced and used, starting from simple analgesics such as acetaminophen, Nonsteroidal anti-inflammatory drug , and opioids to the ergotamine and triptans groups. Triptans are often used, especially in moderate to severe migraine attacks. However, triptans have some contraindications. Triptans are 5-Hydroxytriptamine (5-HT) 5-HT1b and 5-HT1d receptor agonists (Ong and De Felice 2018). The analgesic effect of triptans on the 5-HT1b receptors makes the intracranial blood vessels vasoconstrictive, whereas the effect on the 5-HT1d receptors blocks several vasoactive peptides and proinflammatory cytokines that can stimulate nociceptors. Several studies have shown that triptans have a vasoconstriction effect in other blood vessels, including the coronary arteries, so their safety profile for patients with vascular comorbidities such as coronary artery disease is still questionable (Dodick *et al*., 2020). A new class of drugs that acts on 5-HT1f has been developed, called ditans. Ditans specifically act on the intracranial blood vessels, which is safe for patients with comorbid vascular disease (Mecklenburg *et al*., 2020).

The efficacy and safety of currently available migraine preventive drugs do not meet the expected effect. They are also not specific for migraine, i.e., antiepileptic, antidepressant, and beta-blocker. Various side effects also decrease the patient's adherence rate. Therefore, some new preventive drugs have been developed (Silberstein *et al*., 2012).

Drugs acting on calcitonin gene-related protein (CGRP) have been developed recently and have shown positive results. Monoclonal antibodies against the CGRP and CGRP receptors ef-

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fectively prevent episodic and chronic migraine with minimal side effects. CGRP is known to play a role in migraine pathophysiology. In 2014, anti-CGRP or monoclonal antibodies were developed (Edvinsson *et al*., 2018). Galcanezumab, eptinezumab, fremanezumab, and erenumab are the monoclonal antibodies that have been developed to date. Among them, eptinezumab is the only monoclonal antibody given intravenously, at a dose of 100 mg or 300 mg every 3 months, while others are given subcutaneously (Datta *et al*., 2021).

The Headache Impact Test-6 (HIT-6) is an instrument that was developed to measure various factors that contribute to the headache burden. HIT-6 is often used for migraine. There are six items in HIT-6, which are pain, social functioning, vitality, role functioning, cognitive functioning, and psychological distress. The patients are asked to answer the questions with "never," "rarely," "sometimes," "very often," and "always." HIT-6 scores ranged from 36 to 78. The higher the score, the more significant the impact of migraine on the quality of life. HIT-6 is easy to use, highly reliable, and consistent. Another instrument used for migraine is monthly migraine days (MMD). A high frequency of MMD is associated with a low quality of life, increased medication use, and loss of productivity. The frequency of MMD is a parameter that could be used as a reference in determining the effectiveness of therapy or prophylaxis. HIT-6 and MMD were used in several studies to determine the success rate of migraine therapy (Di Tanna *et al*., 2019; Shin *et al*., 2008).

Many clinical trials about the effectiveness of eptinezumab as a preventive migraine therapy have been conducted. So far, some of these studies have shown positive results. Several researchers have also conducted meta-analyses regarding the efficacy of eptinezumab. However, most of the outcomes they assessed were based only on MMD. Therefore, we conducted an updated meta-analysis to determine the efficacy of eptinezumab (100 mg and 300 mg) as a migraine preventive therapy based on mean MMD and mean HIT-6 scores. In addition, we assessed the safety profile of eptinezumab based on the frequency of the most frequent side effects in each of the available Randomized controlled trial (RCTs).

METHODS

Data sources and search strategy

We systematically searched PubMed and Cochrane Library using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method to prepare this systematic review. We used the keywords "migraine" OR "migraineurs" OR "migrain" OR "migraineous" OR "migrainous" AND "eptinezumab" AND "placebo" OR "placebos" OR "placeboes" on search engines. The Population, Intervention, Comparison, Outcome, and Study design (PICOS) format was used to establish a search strategy. The PICOS and eligibility criteria are shown in Table 1.

Study selection and screening

Titles and abstracts were screened based on the inclusion and exclusion criteria by two authors (first screening). After screening the titles and abstracts, two authors reviewed the selected full text (second screening). If two authors disagreed, the third author was consulted, and a decision was made by consensus. Articles were included in the meta-analysis when data pooling and outcome measurement were identical.

Inclusion and exclusion criteria

For a study to be included, it had to be an English language study, be a randomized clinical trial, have an available full-text article and a complete manuscript, and be published in the last 5 years. Articles in the forms of case reports, descriptive studies, clinical trials, cross-sectional studies, cohort studies, and case-control studies were excluded. The titles and abstracts were manually screened in accordance with the eligibility requirements.

Data items and collection

Three authors collected and extracted data from the selected articles. The data were extracted for the following variables: inclusion criteria, sample size, mean age, intervention, comparison, outcome measurement, duration of intervention, and statistical data. The statistical analysis between the intervention and control group data was calculated using the RevMan software (version 5.4). Confidence intervals and *p*-values were used to calculate the missing standard deviation from each study.

Risk of bias (ROB) and quality assessment

We use the JADAD scale to assess the quality assessment for each study. The JADAD scale is used to assess the methodological quality of clinical trials. The Cochrane ROB tool for RCTs was used to assess the ROB. Two reviewers evaluated the included articles independently. The third reviewer resolved disagreements between the two reviewers.

RESULTS

Literature search

There were 112 article results in PubMed and 150 in Cochrane Library. After removing duplicates, 125 articles were screened based on the titles and abstracts. We used Boolean operators to search the papers. We excluded articles that were not randomized controlled trials and were not published in the last 5 years. The full texts of 18 studies were screened by 2 authors. After screening the full text, eight studies were found eligible and included in this review. The flow of the article search system is shown in Figure 1.

ROB and quality assessment

A moderate ROB was present in almost all included studies. Some studies did not report complete statistical results and reported ambiguous details on the dropout rate. The ROB summary is shown in Figure 2. The quality assessment of each study was done using the JADAD scale. The JADAD scale is used to evaluate the methodological quality of clinical trials. There were five questions with one score for each question. The study with a total score range of 3–5 is high quality, and that with 1–2 is low quality. All studies included in this review were of high quality. The results of the quality assessment are shown in Table 2.

Synthesis results

The sample size ranged from 431 to 1,072, with a mean age ranging from 39.9 to 41.4 years. Each study performed an intervention using eptinezumab at doses of 100 mg and 300 mg

Table 1. PICOS and eligibility criteria.

PICOS	Inclusion criteria	Exclusion criteria
Population (P)	Migraine classified by the ICHD criteria History of migraine >12 months Episodic or chronic migraine	Nonhuman subject, other types of headaches Acute migraine
Intervention (I)	Eptinezumab 100 mg or 300 mg	—
Comparison (C)	Placebo	—
Outcome (O)	MMD HIT-6 Adverse events profile	—
Study design (S)	RCTs Published in last 5 years (2017–2022)	Non-English article Unavailable full-text article Uncompleted article

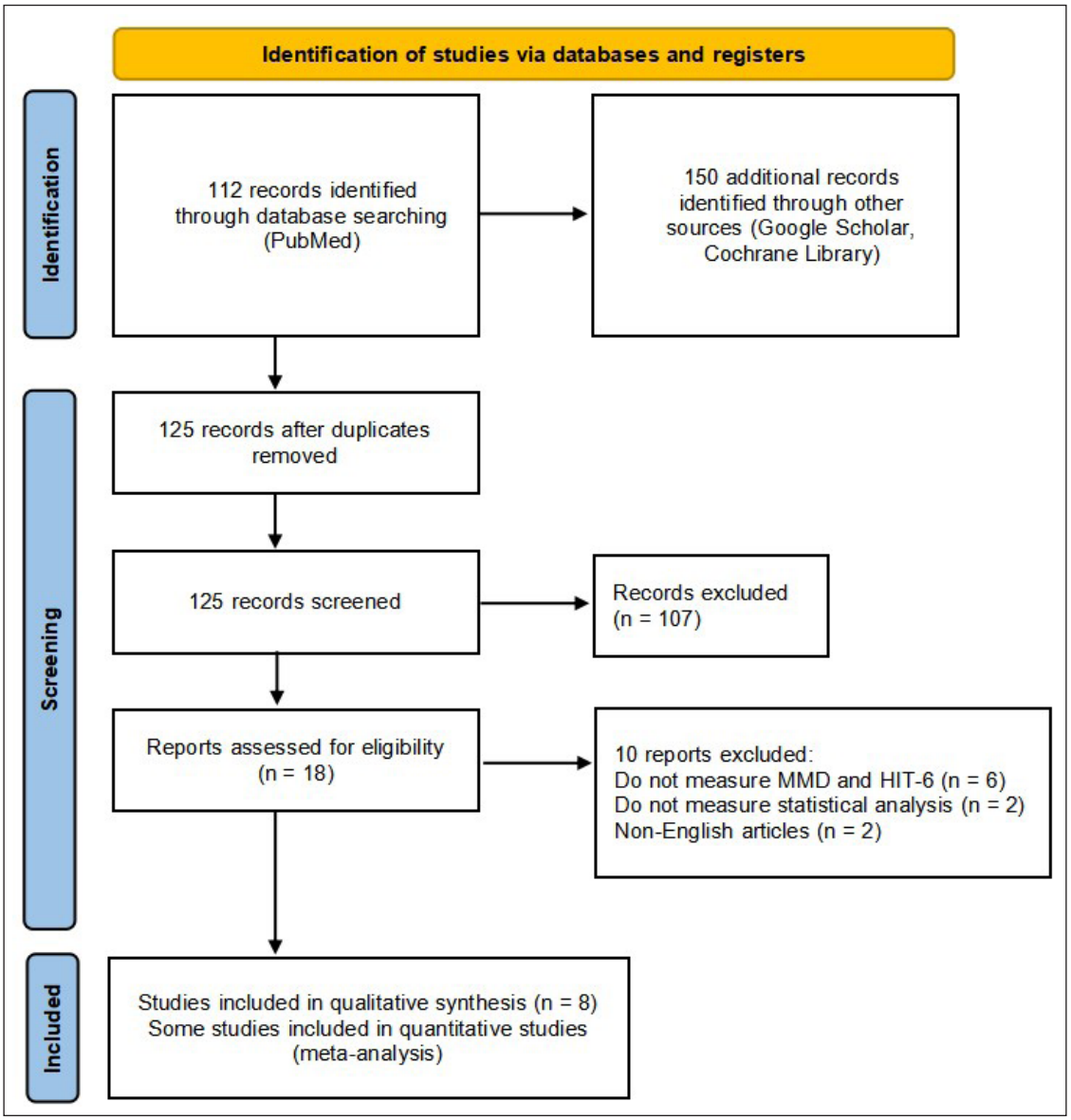

Figure 1. The flow diagram of article search.

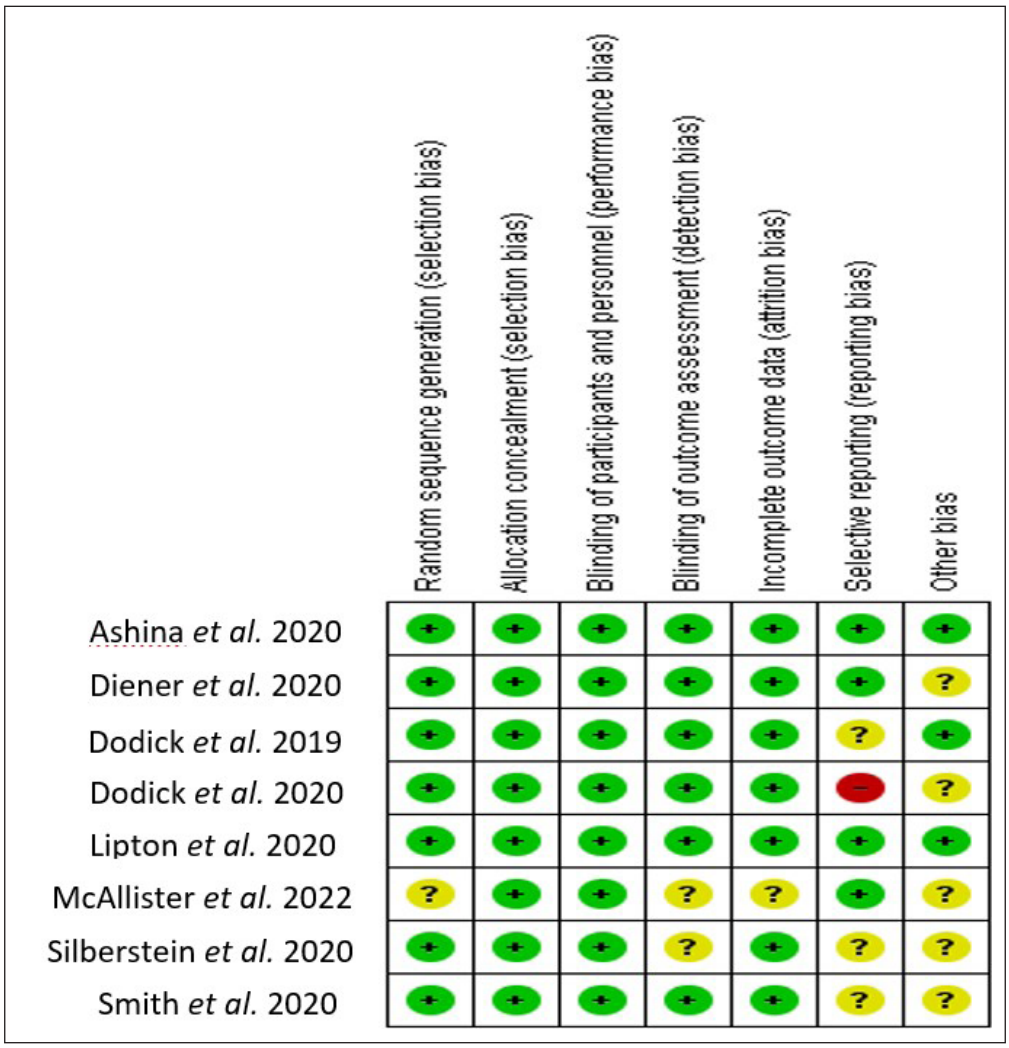

Figure 2. Risk of bias summary.

Table 2. JADAD scale.

Author	Randomization	Blinding	Withdrawals	Total	Quality
Dodick *et al*. 2020	2	2	1	5	High
Tepper *et al*. (2020)	2	2	1	5	High
Lipton *et al*. (2020)	2	2	1	5	High
Diener *et al*. (2020)	2	2	1	5	High
Smith *et al*. (2020)	2	2	0	4	High
Silberstein *et al*. (2020)	2	1	0	3	High
Dodick *et al*. (2020)	2	2	0	4	High
McAllister *et al*. (2022)	1	1	1	3	High

and had cut-off periods of 12 weeks and 24 weeks. MMD, HIT-6, and adverse events during the intervention were assessed. A summary of the study characteristics of the sample size, mean age, type, and duration of intervention from each study is shown in Table 3.

Main pooled results of meta-analysis

Studies with identical data and the same outcome measure were calculated for meta-analysis. A meta-analysis study was conducted to compare the results of the mean MMD difference between the intervention (eptinezumab 100 mg and 300

Table 3. Summary of the study characteristics.

Author	Inclusion criteria	Sample size (*n*)	Mean age	Intervention	Comparison	Duration of intervention (weeks)	Measurement
Tepper *et al*. (2020)	Adults aged 18–75 years diagnosed with migraine according to the ICHD criteria History of migraine >12 months with <14 headache days per month	888	39.8 (11.39)	Eptinezumab 30 mg (*n* = 219) 100 mg (*n* = 223) 300 mg (*n* = 224)	Placebo (*n* = 222)	12	MMD AE
Lipton *et al*. (2020)	Adults aged 18–65 years diagnosed with migraine before 50 years old Had history of CM >12 months	1,072	40.5 (11.2)	Eptinezumab 100 mg *n* = 356 300 mg *n* = 350	Placebo *n* = 366	12	MMD HIT-6 AE
Diener *et al*. (2020)	Adults diagnosed with migraine according to the ICHD criteria before 50 years old, >12 months	431	41.4 (10.78)	Eptinezumab 100 mg *n* = 139 300 mg *n* = 147	Placebo *n* = 145	24	MMD AE
Smith *et al*. (2020)	Adults aged 18–75 years diagnosed with migraine according to the ICHD criteria before 50 years old, >12 months	888	39.8	Eptinezumab 30 mg *n* = 223 100 mg *n* = 221 300 mg *n* = 222	Placebo *n* = 222	48	MMD AE
Silberstein *et al*. (2020)	Adults aged 18–65 years diagnosed with migraine according to the ICHD criteria before 50 years old >12 months	1,072	40.5 (11.2)	Eptinezumab 100 mg *n* = 356 300 mg *n* = 350	Placebo *n* = 366	24	MMD AE
Dodick *et al*. (2020)	Adults aged 18–55 years diagnosed with migraine according to the ICHD criteria before 35 years old >12 months	669	39.8	Eptinezumab 100 mg *n* = 223 300 mg *n* = 224	Placebo *n* = 222	12	MMD
Dodick *et al*. (2020)	Adults aged 18–55 years diagnosed with migraine according to the ICHD criteria before 35 years old >12 months	616	—	Eptinezumab 10 mg *n* = 130 30 mg *n* = 122 100 mg *n* = 122 300 mg *n* = 121	Placebo *n* = 121	12	MMD HIT-6 AE
McAllister *et al*. (2022)	Adults aged 18–75 years diagnosed with migraine according to the ICHD criteria before 50 years old	480	—	Eptinezumab 100 mg *n* = 238	Placebo *n* = 242	4	HIT-6

MMD: monthly migraine days; AE: adverse events; HIT-6: Headache impact test-6.

mg) and placebo at the cut-off durations of 12 weeks and 24 weeks and the mean difference between before and after intervention (eptinezumab 100 mg and 300 mg). The mean difference in the mean HIT-6 score was also calculated between the intervention (eptinezumab 100 mg) and placebo groups and the pre-and postintervention groups.

Monthly migraine days

The mean differences in MMD were compared between eptinezumab 100 mg and placebo at 12 weeks and 24 weeks (after intervention), eptinezumab 300 mg and placebo at 12 weeks and 24 weeks (after intervention), and also between baseline mean MMD (before intervention) and mean MMD after 12 weeks and 24 weeks (after intervention) of eptinezumab 100 mg and eptinezumab 300 mg.

Eptinezumab 100 mg versus placebo

Following a 12-week intervention, the mean MMD difference between eptinezumab 100 mg and placebo is shown in Figure 3A. The pooled mean difference in the mean MMD is −1.52 (95% CI −2.27 to −0.076, *p* 0.0001). Figure 3B shows the mean MMD difference between eptinezumab 100 mg and placebo after 24 weeks of intervention using a pooled random-effect data model. When the data from three studies with the same data are combined, the pooled mean difference in the mean MMD is −1.89 (95% CI −3.26 to −0.52, *p* = 0.007). The mean MMD decreased more significantly when eptinezumab 100 mg was used for 24 weeks than 12 weeks.

Eptinezumab 300 mg versus placebo

Figure 3C shows the mean MMD difference between eptinezumab 300 mg and placebo after 12 weeks of intervention using a pooled random-effect data model. The pooled mean difference in mean MMD for five studies with identical data is 1.90 (95% CI −2.8 to −0.99, *p* 0.0001). Figure 3D displays the mean MMD difference between eptinezumab 300 mg and placebo after 24 weeks of intervention using a pooled random-effect data model. The pooled mean difference in mean MMD for three

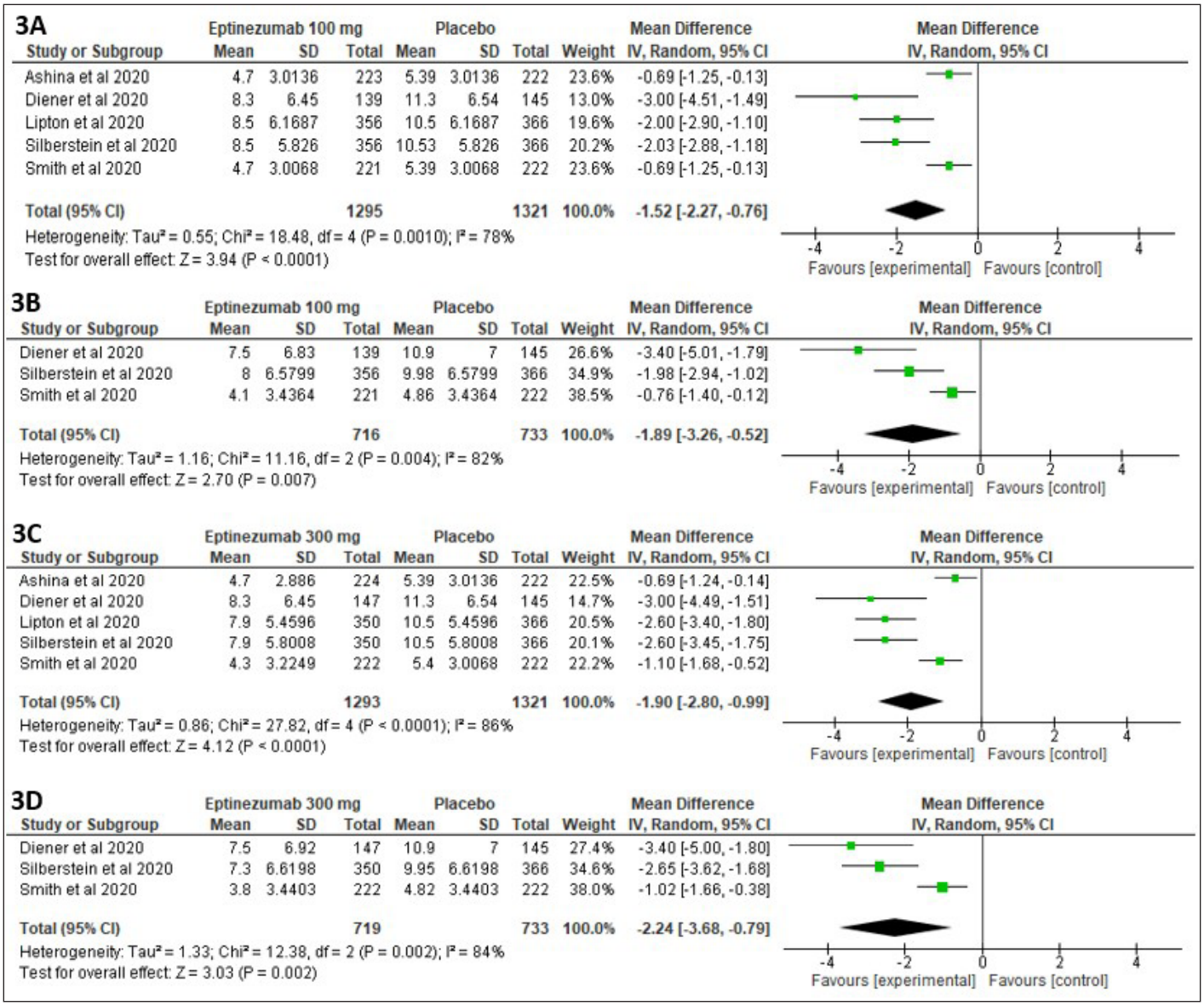

Figure 3. Pooled data comparing mean differences in mean MMD between eptinezumab 100 mg and placebo group at 12 weeks (A) and at 24 weeks (B) and eptinezumab 300 mg and placebo group at 12 weeks (C) and at 24 weeks (D).

studies with identical data is −2.24 (95% CI −3.68 to −0.79, p = 0.002). The MMD rate was decreased more by using eptinezumab 300 mg for 24 weeks than 12 weeks.

Eptinezumab before and after intervention

The mean MMD difference between eptinezumab 100 mg before intervention and eptinezumab 100 mg after 12 weeks of intervention is shown in Figure 4A using a pooled random-effect data model. The pooled mean difference in the mean MMD for two studies with identical data for meta-analysis is −6.16 (95% CI −10.47 to −1.85, p = 0.005). The mean MMD difference between eptinezumab 300 mg before intervention and eptinezumab 300 mg after 12 weeks of intervention is shown in Figure 4B using a pooled random-effect data model. The pooled mean difference in mean MMD for two studies with identical data for meta-analysis is −6.4 (95% CI −10.61 to −2.19, p 0.00001). The use of eptinezumab 300 mg was superior to eptinezumab 100 mg in reducing the mean MMD for 12 weeks.

Headache impact test-6 score

Figure 5A shows the mean difference in HIT-6 score between eptinezumab 100 mg and placebo after 12 weeks of intervention using a pooled random-effect data model. The pooled mean difference in the mean HIT-6 score for two trials with similar data for meta-analysis is −2.87 (95% CI −3.78 to −1.96, p 0.00001). Figure 5B shows the mean difference in mean HIT-6 score between eptinezumab 100 mg before intervention (baseline) and eptinezumab 100 mg after 12 weeks of intervention using a pooled random-effect data model. The pooled mean difference in the mean HIT-6 score for two trials with similar data for meta-analysis is −7.36 (95% CI −8.25 to −6.48, p 0.00001). Using eptinezumab 100 mg for 12 weeks decreased the mean HIT-6 score significantly.

Adverse events

Adverse events were reported in some populations during the intervention. The summarized results of the incidence of any events at each dose (Fig. 6) showed that there was no significant

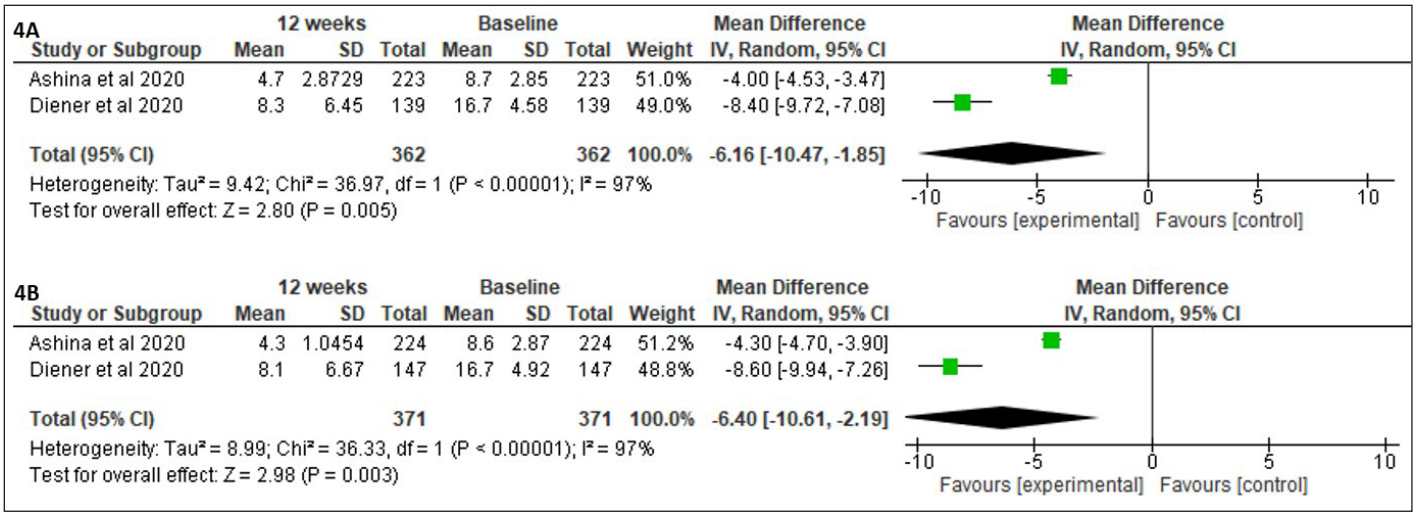

Figure 4. Pooled data comparing mean differences in mean MMD between eptinezumab 100 mg before intervention (baseline) and eptinezumab 100 mg after 12 weeks of intervention (A) and eptinezumab 300 mg before intervention (baseline) and eptinezumab 300 mg after 12 weeks of intervention (B).

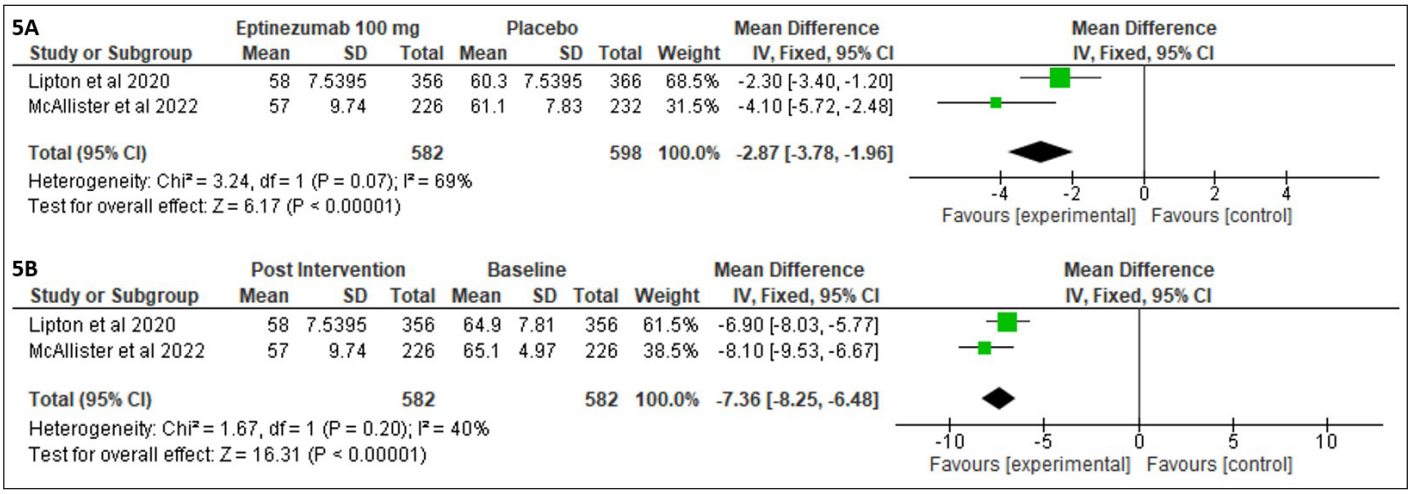

Figure 5. Pooled data comparing mean differences in mean HIT-6 score between eptinezumab 100 mg and placebo after 12 weeks of intervention (A) and eptinezumab 100 mg before intervention (baseline) and eptinezumab 100 mg after 12 weeks of intervention (B).

difference between eptinezumab 100 mg and 300 mg ($p = 0.07$). The most frequently reported adverse events were nasopharyngitis ($n = 245$), followed by upper respiratory tract infection ($n = 237$), sinusitis ($n = 42$), dizziness ($n = 44$), and urinary tract infection ($n = 37$). No deaths were reported in these studies. The incidence of side effects at each dose of eptinezumab and placebo can be seen in Table 4.

DISCUSSION

Eptinezumab is the only CGRP monoclonal antibody available intravenously and has a bioavailability of 100%. Steady-state plasma concentrations can be achieved after the first dose. Eptinezumab is not metabolized by cytochrome P450 and is not affected by other drug interactions. Several studies have shown that the administration of sumatriptan does not decrease the concentration and effectiveness of eptinezumab (Datta *et al*., 2021). The recommended dose of eptinezumab is 100 mg or 300 mg every 3 months. Some patients require a dose of 300 mg. Eptinezumab is given intravenously in 100 ml of a 0.9% NaCl solution for 30 minutes, so its administration requires professional healthcare (Morgan and Joyner 2021).

A study shows that those with more frequent MMD have a lower quality of life, lower productivity, and a high burden of maintenance costs (Johnston *et al*., 2022). Our meta-analysis showed that the administration of eptinezumab decreased the mean MMD. Administration of eptinezumab 100 mg and 300 mg reduced the mean MMD more than placebo in 12 and 24 weeks. Between the periods before and after intervention, eptinezumab 300 mg reduced the mean MMD more than eptinezumab 100 mg (−6.16 *vs*. −6.40). Smith *et al*. (2020) reported that the proportion of patients who experienced >50% and >75% symptom improvement was more significant at 24–48 weeks than at 1–24 weeks. Continuous administration after the first dose (12 weeks) has a better effect and is relatively safe with minimal side effects (Smith *et al*., 2020).

The HIT-6 score was created to screen and monitor patients with headaches for clinical and research purposes. The HIT-6 score assesses the effects of headaches on pain, social

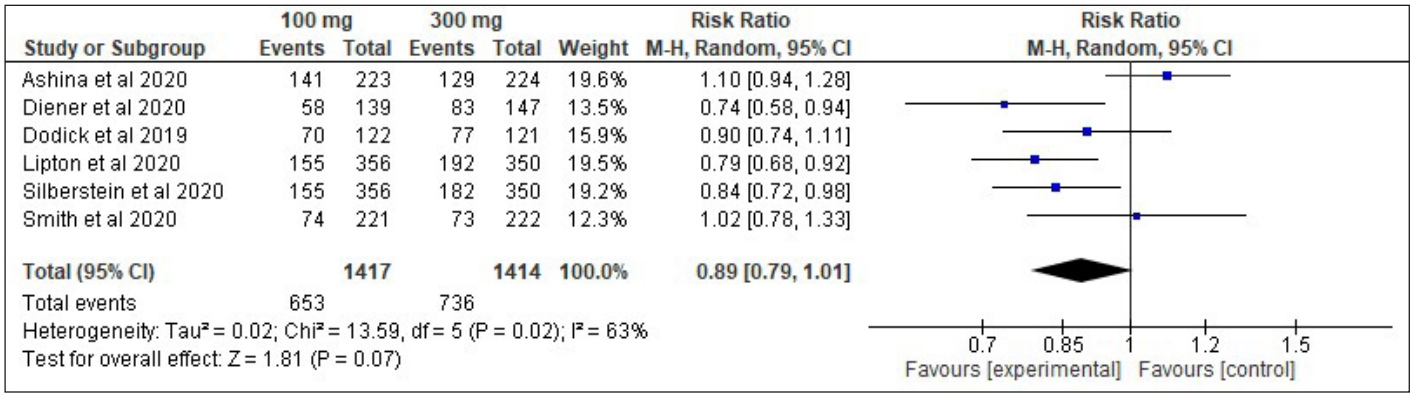

Figure 6. Pooled risk ratio of any events between eptinezumab 100 mg and 300 mg.

Table 4. Adverse events that occurred during the intervention period.

	100 mg		300 mg		Placebo		Total
Any events	653	32.5%	736	36.7%	617	30.8%	2,006
Top 5 adverse events:							
Nasopharyngitis	76	3.78%	107	5.33%	62	3.1%	245
Upper respiratory tract infection	77	5.4%	98	4.89%	62	3.09%	237
Sinusitis	19	0.95%	32	1.60%	42	2.09%	93
Dizziness	28	1.40%	8	0.40%	8	0.40%	44
Urinary tract infection	11	0.55%	20	1.00%	6	0.30%	37

functioning, vitality, role functioning, cognitive function, and psychological distress. The HIT-6 score has been validated and used globally to monitor treatment efficacy for headaches, including migraine (Yang *et al*., 2011). Our meta-analysis showed that the mean HIT-6 score between eptinezumab 100 mg and placebo was −2.87 (95% CI −3.78 to −1.96, $p < 0.00001$). Meanwhile, the mean HIT-6 score before and after intervention of eptinezumab 100 mg after the first dose (12 weeks) was −7.36 (95% CI −8.25 to −6.48, $p < 0.00001$). This shows that eptinezumab 100 mg improves the quality of life and daily functioning. In the Prevention of Migraine via Intravenous ALD403 Safety and Efficacy (PROMISE) PROMISE-2 study, at 4 weeks, eptinezumab 100 mg and eptinezumab 300 mg significantly reduced the mean HIT-6 scores (Lipton *et al*., 2021).

Side effects after taking eptinezumab have been reported in several studies. Based on the PROMISE-1 and PROMISE-2 trials, nasopharyngitis and upper respiratory tract infection were the most common side effects after taking eptinezumab. In the PREVAIL trial, adverse events occurred in about 71% of the participants. The most common side effects are nasopharyngitis, upper respiratory tract infection, sinusitis, and influenza. In this trial, three participants were pregnant during the intervention period, two of whom miscarried (Kudrow *et al*., 2021). This report is in line with the results of our meta-analysis. In our meta-analysis, the incidence of side effects was 653 (46.1%) in eptinezumab 100 mg and 736 (52.1%) in eptinezumab 300 mg. The most frequently reported side effects were nasopharyngitis, upper respiratory tract infection, sinusitis, dizziness, and urinary tract infection (Table 4). The side effects reported in this review were consistent with those in previous studies of eptinezumab for migraine. There was no significant difference in the incidence of side effects between eptinezumab 100 mg and 300 mg ($p = 0.07$). The PREVAIL trial also revealed that eptinezumab 300 mg was the maximum safe and tolerable dose (Tassorelli *et al*., 2018). The incidence of placebo side effects is mostly related to patient and doctor expectations and disease-specific symptoms (Weihrauch and Gauler, 1999).

Based on the above results, eptinezumab is effective and safe as a migraine preventive therapy. Eptinezumab 300 mg was more effective in reducing the mean MMD and HIT-6 scores, with no significant difference in the incidence of side effects from eptinezumab 100 mg. The use of eptinezumab 300 mg can be considered a preventive therapy for moderate to severe migraine without fear of side effects.

More studies with variations in population types are needed to strengthen the results of the eptinezumab study. In addition, the cost of a single infusion of eptinezumab is known to reach $1,600 (every 3 months). However, these costs are insignificant compared to the improvement of the daily functioning impact caused by migraine (Datta *et al*., 2021). Previous studies have shown that eptinezumab can be effective for up to 48 weeks. There needs to be a more comprehensive study on whether eptinezumab can be effective and safe for at least the next 3–5 years, considering that migraine is a chronic disease. Other CGRP monoclonal antibodies, such as erenumab and fremanezumab, have been tested to this point (Tepper *et al*., 2020).

CONCLUSION

Eptinezumab is safe and effective as a migraine preventive therapy. Eptinezumab reduces the mean MMD and HIT-6 scores, and there was no significant difference in the incidence of side effects between eptinezumab 100 mg and 300 mg. Eptinezumab can be considered a preventive therapy for episodic and chronic migraine.

LIMITATIONS

There were not enough studies included in this systematic review. Future research on the efficacy and safety of eptinezumab for migraine needs to be carried out.

AUTHORS' CONTRIBUTIONS

IMO conceived the idea to carry out this systematic review. IMO is a neurologist and a headache consultant. EHT and IPE performed the study search and data extraction and were approved by IMO. EHT calculated the data for the meta-analysis using RevMan. The results of the meta-analysis calculations were then checked by IPE and confirmed by IMO. EHT prepared this manuscript. IMO and IPE then read and revised the manuscript. The three authors reread the final results of the manuscript and reached a consensus.

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CONFLICTS OF INTEREST

The authors report no financial or other conflicts of interest in this work.

FUNDING

There is no funding to report.

ETHICAL APPROVAL

No ethical approval was required for this study.

DATA AVAILABILITY

All data generated and analyzed are included in this article.

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ABBREVIATIONS

5-HT, 5-Hydroxytriptamine; CGRP, Calcitonin gene-related protein; HIT-6, Headache Impact Test-6; MMD, Monthly migraine days; NSAID, Nonsteroidal anti-inflammatory drug; RCT, Randomized controlled trial; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROMISE, Prevention of Migraine via Intravenous ALD403 Safety and Efficacy; PICOS, Population, Intervention, Comparison, Outcome, and Study design.

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