

# Prevalence of Migraine in Saudi Arabia and the Proposed Introduction of Eptinezumab: A Pooled and Meta-Analysis from Clinical Trials

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## ABSTRACT

**Introduction:** Chronic migraines (CM) affect a significant portion of the Saudi population, yet patients lack access to Eptinezumab, a drug with proven preventive efficacy and a strong safety record. This analysis aims to evaluate Eptinezumab's effectiveness in managing CM and advocate for its availability to Saudi patients.

**Methods:** We performed a meta-analysis of data from two clinical trials registered on ClinicalTrials.gov (Identifiers: NCT02275117 and NCT02974153), involving patients treated with 100mg or 300mg doses of Eptinezumab or a placebo, delivered through IV infusion.

**Results:** The analysis included data from over 1400 individuals, revealing that Eptinezumab significantly reduces MMDs, with the 300mg dosage being more effective than the 100mg. The 300mg dose reduced MMDs by an average of -8.2 days, while the 100mg dose achieved a reduction of -7.7 days.

**Discussion:** Our findings confirm the substantial benefits of Eptinezumab in reducing the burden of CM, with both dosages showing effectiveness. The 300mg dose, in particular, provides a greater reduction in MMDs. These results, paired with the drug's excellent safety profile, suggest that Eptinezumab would be a valuable addition to the treatment options available to Saudi patients.

**Conclusion:** The administration of Eptinezumab at the studied dosages demonstrates prolonged preventive effects on CM with minor side effects. This supports the potential for introducing Eptinezumab in Saudi Arabia, proposing it as a promising CM treatment to improve patient outcomes.

**Keywords:** Eptinezumab, Headache, Migraine, Meta-Analysis, Saudi Arabia

## Introduction

Migraine is marked by recurrent, often unilateral pulsating headaches, typically with nausea and sensitivity to light and sound. The trigeminovascular system plays a key role in migraine pain, involving trigeminal ganglia neurons, cerebral arteries, and meningeal arteries [1].

Migraines are classified into several types including migraine with aura, without aura, chronic migraine (CM), and episodic migraine (EM). CM is defined by having 15 or more headache days per month over 3 months, with at least 8 days exhibiting migraine features like unilateral pulsating pain with moderate-to-severe intensity, often accompanied by nausea, vomiting, light and sound sensitivity, and possibly aura. CM can greatly affect daily functioning and is often associated with psychiatric

disorders and medication overuse headaches [2]. Migraine headaches cost the US approximately \$17 billion annually, mainly from outpatient care and loss of workplace productivity [3].

Migraine prevalence varies globally. In US, migraines led to about 4 million ER visits in 2016 [4]. Europe had a 1-year prevalence of 14%, peaking between ages 20 and 50 [5].

The incidence of migraine in Saudi Arabia is high, reaching up to 20%, but comprehensive research on its prevalence across the general population is lacking [6-11]. There's also a gap in data regarding the effectiveness and safety of migraine treatments among Saudi patients and their small sample sizes limit their conclusiveness, pointing to a need for more extensive research.

Eptinezumab is not yet approved for migraine management in Saudi Arabia, but its efficacy and safety are increasingly

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supported by evidence. It has been approved in USA and is currently under review by the Canadian FDA for migraine prevention [12]. No previous meta-analyses have conducted on Eptinezumab's efficacy. The goal of this study is to compile and analyze meta-analytic data on the effectiveness of Eptinezumab in treating migraines, drawing from existing clinical trials. The findings may motivate the Saudi FDA to initiate a clinical trial for Eptinezumab among Saudi patients and contemplate its approval in the country. The study also provides a brief overview of current and novel therapies for migraine.

## Methodology

### Study Design/data analysis

This review was a mixed-methods study, incorporating both quantitative and qualitative approaches. The quantitative component evaluated the prevalence of migraine in Saudi Arabia,

while the qualitative part assessed the efficacy of Eptinezumab in treating migraines through patient and healthcare provider testimonials. Research databases such as PubMed, EMBASE, and the Cochrane Library were searched using specific keywords. Descriptive statistics were used to calculate the prevalence rates. Data analyses were conducted using IBM® SPSS26® software. Only publicly available data from prior studies were used, which did not require separate ethical approval.

### Search Strategy

The search strategy for the meta-analysis aimed at identifying all clinical trials evaluating the efficacy and safety of Eptinezumab in CM patients. A comprehensive search was conducted on the ClinicalTrials.gov database using the specific identifiers for the relevant clinical studies. (Table 1)

**Table 1: Summaries for the clinical trials on Eptinezumab which were conducted on patients with migraine.**

Study	Phase	Number of patients	Study design	Drug doses in the study
NCT02559895	Three	888	Double-blind, randomized, placebo-controlled, parallel group	Eptinezumab 30 mg, 100mg, or 300mg, or placebo
NCT01772524	One	163	Double-blind, randomized, placebo-controlled, parallel group	Eptinezumab 1000mg or placebo
NCT02985398	Three	128	Open-label, uncontrolled	Eptinezumab 300mg
NCT02275117	Three	616	Double-blind randomized, placebo-controlled, parallel group	Eptinezumab 10mg, 30mg, 100mg, 300mg, or placebo
NCT02974153	Three	1072	Double-blind randomized, placebo-controlled, parallel group	Eptinezumab 100mg, 300mg, or placebo

Inclusion Criteria were IV Eptinezumab at 100mg or 300mg, or placebo comparisons trials in CM patients that reports Efficacy (e.g., monthly migraine days (MMDs) reduction) with all safety and adverse events data.

Exclusion Criteria were non-CM-focused trials or studies not assessing Eptinezumab or using non-IV administration and studies that Lack of explicit efficacy/safety outcomes.

The database was queried for detailed information on trial design, patient demographics, intervention specifics, outcomes, and adverse events related to the use of Eptinezumab.

### Statistical Analysis

The statistical analysis for the pooled data from the clinical trials was conducted using a meta-analytic approach. The primary efficacy endpoint was the change from baseline in the mean number of MMDs. Secondary endpoints included the proportion of patients experiencing a 50% or greater reduction in MMDs, and changes in acute medication use.

For the efficacy analysis, weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for continuous outcomes, while risk ratios (RRs) with 95% CIs were calculated for dichotomous outcomes. The safety analysis evaluated the incidence of adverse events, comparing Eptinezumab with placebo, and reported as risk differences with 95% CIs.

All statistical analyses were performed using Cochrane Review Manager (RevMan 5.4) software, and a p-value of less than 0.05 was considered statistically significant.

### Results

Two clinical trials (NCT02275117 and NCT02974153) involving 1436 individuals with CM were analyzed. In the study, 949 participants were administered Eptinezumab and 487 received a placebo. Of the Eptinezumab group, 478 received 100mg and 471 received 300mg. A high adherence to the treatment protocol was noted, with 98.88% (1420 patients) completing the protocol and only 1.11% (16 patients) withdrawing within the first 12 weeks, due to various reasons including withdrawal of consent, loss to follow-up, failure to meet study criteria, or multiple protocol violations.

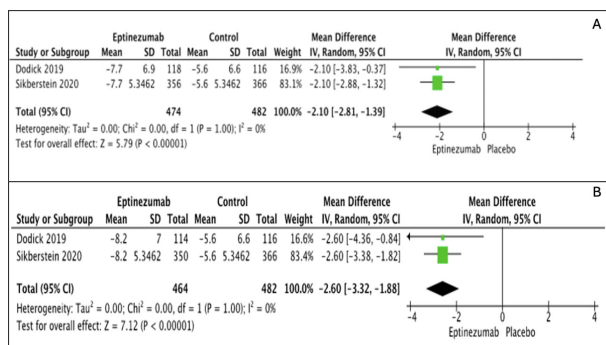
The demographic and baseline characteristics indicated an average age of 38.7 years with a majority being female (86.78%) and White (91%). (Table 2) Participants had a long-standing history of migraine, averaging 18.2 years, and reported an average of 20.88 headache days, including 16.36 MMDs, during the 28-day screening period. More than half of the participants (56.82%) were not in a state of medication overuse, while 43.17% were classified as having medication overuse headache.

**Table 2: The baseline characteristics and demographics of the Two clinical trials (NCT02275117 and NCT02974153). BMI: body mass index.; SD: standard deviation.; A.M.: African American**

Demographic	Placebo	Eptinezumab 300mg	Eptinezumab 100mg
Safety population	487	471	478
Efficacy population	482	464	474
Age, mean (SD), years	38.4 (10.25)	39.1 (10.2)	38.85 (10.55)
Sex: Women, n (%)	434 (89.4)	412 (85.35)	411 (85.6)
Race, n (%)			
• White	430 (88.85)	436 (93)	440 (91.15)
• Black/A.M*	45 (8.2)	27 (4.8)	33 (7.95)
• Others	12 (2.95)	8 (2.2)	5 (0.9)
Ethnicity, n (%)			
• Hispanic or Latino	51 (11.3)	36 (10.05)	56 (14.15)
• NOT Hispanic or Latino	436 (88.7)	435 (89.95)	422 (85.85)
• BMI *, mean (SD), kg/m <sup>2</sup>	27.3 (5.75)	26.75 (5)	27.15 (5.15)
• Years since diagnosis, mean (SD)	17.8 (10.9)	18.9 (10.7)	17.85 (11.5)
Mean per 28 days, n (%)			
• Migraine days (SD)	16.3 (4.8)	16.3 (4.8)	16.5 (4.7)
1. Headache days (SD)	20.85 (3.54)	20.75 (3.5)	21.05 (3.5)
• Medication over use headache, n (%)	104.5 (46.3)	106 (48)	99.5 (44)

The meta-analysis revealed that both 100mg and 300mg doses of Eptinezumab significantly reduced MMDs compared to placebo. For the 100mg dose, the mean reduction was -2.10 days with a 95% confidence interval of (-2.88, -1.39) and P < 0.00001. For the 300mg dose, the reduction was even greater, with a mean difference of -2.60 days and a 95% confidence interval of (-3.32, -1.88) and P < 0.00001. These results, underscore the efficacy of Eptinezumab in reducing the frequency of MMDs. (Figure 1)

**Figure 1B:** showing the total efficacy outcome of 2 arms groups of Eptinezumab 300mg (n=464) and placebo (n=482). The reduction of migraine days was taken after 12 weeks in both studies. Green color represents the estimated effect. Black diamond represents the overall estimate. The width of the diamond represents the 95% confidence interval with {-3.32, -1.88}. Sikberstein et al. represents high weight estimation of 83.4%. CI; Confidence interval; SD: standard deviation.



**Figure 1A:** showing the total efficacy outcome of 2 arms groups of Eptinezumab 100mg (n= 474) and placebo (n=482). The reduction of migraine days was taken after 12 weeks in both studies. Green color represents the estimated effect. Black diamond represents the overall estimate. The width of the diamond represents the 95% confidence interval with {-2.81, -1.39}. Sikberstein et al. represents high weight estimation of 83.1%. CI; Confidence interval; SD: standard deviation.

**Discussion**

**Part 1 - brief review**

**1. Overview of current therapies for migraine.**

Nearly all migraine sufferers (98%) use acute treatments, with half relying on OTC drugs like aspirin and NSAIDs, and others using prescription medications. Abortive treatments are common for immediate relief, whereas severe cases may need prescription drugs including opioids, which are linked to negative health outcomes when used regularly [13-15].

Preventive migraine therapy, targeting a reduction in attack frequency and severity, is underutilized, with only about 5% of patients undergoing such treatment [16]. Effective prevention can cut attack frequency by 50% and involves pharmacological agents like beta-blockers, anticonvulsants, and antidepressants, alongside lifestyle adjustments such as stress management and sleep improvement [2,17]. Table 3 summarizes the most used groups.

**Table 3: Overview of current therapies for migraine.**

	Drug	Mechanism of action	Notes
<u>Abortive Treatments</u>	Paracetamol	It inhibits COX-1 and COX-2 via the peroxidase activity of these isoenzymes. This inhibits the generation of phenoxyl radicals from a key tyrosine residue required for COX-1 and COX-2 action, as well as prostaglandin (PG) synthesis. The 'COX3 theory,' which attributes paracetamol's efficacy to its unique suppression of a third cyclooxygenase isoform enzyme, has lost confidence in recent years and is a central mode of action for paracetamol is now considered more likely.	In migraines, 1g of paracetamol provides complete relief for 19% of patients within two hours—superior to placebo's 10%—and lessens pain to mild for 56%, versus placebo's 36% [18].
	NSAIDs	It suppresses cyclooxygenase (COX1 and COX2) activity, which catalyzes the generation of prostaglandins accountable for pain and inflammation.	A 400mg dose of Ibuprofen offers complete pain relief for 26% of patients, and 57% see pain reduced to mild within two hours, outperforming placebo [19]. Aspirin, used since the 1980s for migraine prevention, is cost-effective despite potential GI and renal side effects, with limited studies on its migraine-specific benefits [20]
	Triptans	They exert their action by constricting the dilated extracerebral cranial blood arteries, most likely through 5-HT <sub>1B</sub> receptors. Additionally, triptans can suppress neuropeptide release and plasma protein extravasation through dural arteries, as well as central trigemino-vascular impulse transmission.	They are recommended by The US Headache Consortium for moderate to severe migraines or when analgesics fail [21]. Combining sumatriptan with NSAIDs like naproxen can enhance relief but doesn't significantly outperform sumatriptan alone, and is most effective when taken early in the migraine's onset [15].
<u>Preventive Treatments</u>	Propranolol	It blocks beta-1 and beta-2 receptors, increases vascular tone by preventing vasodilation, thus reducing migraine occurrence. Also, by inhibiting trigeminal nociception via antagonising $\beta$ 1 receptors on thalamocortical neurons. As a result, $\beta$ -blockers may exert a therapeutic effect on thalamic neurotransmission in migraine. Sensory processing impairments in the thalamus and cortex may account for several other classic migraine manifestations, like photophobia and phonophobia.	Propranolol is endorsed in guidelines for migraine prophylaxis due to its effectiveness in reducing MMDs and its strong safety profile [22].
	Amitriptyline	Amitriptyline possesses combined serotonergic and noradrenergic reuptake inhibitory characteristics (SNRI), which boosts the efficacy of diffuse noxious inhibitory control. Additionally, Amitriptyline also has additional pharmacological modes of action. These include adenosine-A1 agonism, which enhances descending regulation of rostral-ventromedial nucleus (RVM) neurons; and boosts GABA-mediated inhibition by favourable regulating the GABA <sub>A</sub> receptor and inhibiting GAT-1 and GAT-3.	In a meta-analysis, Amitriptyline was found to be significantly more effective than placebo, with longer treatment periods leading to better results, and this efficacy was observed in both larger and smaller study groups [23].
	Topiramate	TPM has been shown to suppress neuronal hyperexcitability via a variety of mechanisms, including blockade of voltage-gated sodium channels, antagonistic properties at glutamate receptors of the AMPA/kainate subtype, state-dependent inhibition of L-type voltage-activated calcium channels, and modulatory action on GABA <sub>A</sub> receptors on GABA-induced chloride currents. TPM also suppresses carbonic anhydrase activity on isozymes II and IV. However, its precise nociceptive effect in migraine is unknown.	Despite its potential efficacy based on its pharmacological actions, the effect of Topiramate on the transition from high-frequency episodic to CM remains uncertain [24]. A clinical trial comparing Topiramate and Amitriptyline to placebo found no significant differences in terms of reducing headache-related disability, frequency of headaches, or treatment completion rates over 24 weeks [25].

## 2. The novel therapeutic options for migraine.

### Calcitonin gene-related peptide (CGRP) Antagonist

CGRP antagonists like Olcegepant and Telcagepant are potential acute migraine treatments without the vasoconstrictive effects of triptans, making them safer for patients with cardiovascular concerns [18]. Telcagepant can be taken orally and is well-tolerated, but concerns over liver enzyme elevations may limit its long-term use [19].

### Calcitonin gene-related peptide (CGRP) antagonists - monoclonal antibody (mAb)

Eptinezumab is a humanized IgG1 monoclonal antibody targeting CGRP, produced using *Pichia pastoris* yeast, and binds to both  $\alpha$  and  $\beta$  forms of human CGRP with high affinity (KD 20 pM) [20]. It blocks the CGRP pathway, providing a recognized method for both acute and preventive migraine treatment [21]. Clinical trials have shown that IV Eptinezumab at doses of 100mg and 300mg is effective for migraine prevention in adults with CM, demonstrating a significant reduction in migraine occurrence from day 1 and an acceptable safety profile. Over half of the patients experienced a substantial decrease in migraine frequency from the baseline, and more than one-third achieved a 75% reduction in MMDs within the first month. These benefits, including patient-reported outcomes, were noted as early as the first month [21,22]. Beyond CM, Eptinezumab is also effective in managing EM, as demonstrated by several clinical studies [23-26]. Regarding safety, Eptinezumab has been associated with a low incidence of treatment-emergent adverse events (TEAEs), such as nasopharyngitis, upper respiratory tract infections, and nausea. Hypersensitivity reactions post-drug administration are typically mild to moderate and can be effectively managed using antihistamines or corticosteroids for one day [27]. Overall, these factors contribute to the high safety profile of Eptinezumab.

### Botulinum Toxin

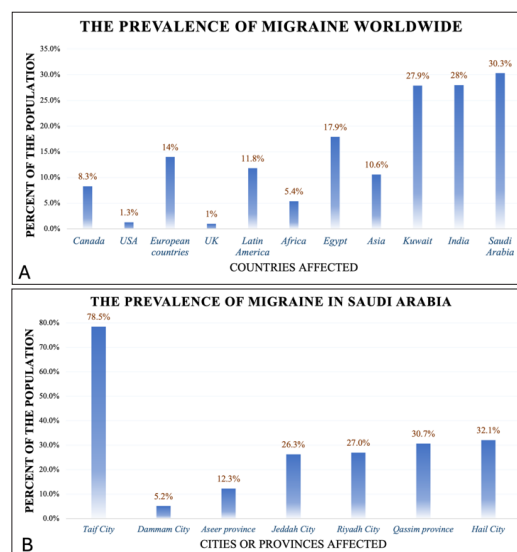
A meta-analysis highlighted its effectiveness in reducing CM frequency after 2 months and improving life quality after 3 months, with a slightly higher risk of adverse events in patients receiving the toxin (risk ratio of 1.32,  $p = 0.002$ ) [28]. In Saudi Arabia, its use for CM prophylaxis has proven efficient and safe [17].

### Part 2 - meta-analysis

The pooled data from two clinical trials showed that a single IV Eptinezumab every 12 weeks was effective in managing adults CM. The analysis involves over 1400 patients indicated that Eptinezumab at both 100mg and 300mg doses has effectively reduced MMDs, with the 300mg dose achieving a greater reduction, averaging -8.2 days, compared to -7.7 days for the 100mg dose, making it more preferred by patients.

Further meta-analysis comparing the two doses establishing that Eptinezumab 300mg was significantly more effective than the 100mg dose, reducing MMDs by an average of -2.60 days (95% CI {-3.32, -1.88};  $P < 0.00001$ ) versus -2.10 days for the 100mg dose (95% CI {-2.81, -1.39};  $P < 0.00001$ ). The placebo response observed in the clinical trials could be attributed to factors such as the method of delivery, frequency of site visits, patient expectations, or other contextual elements. Despite the placebo effect, Eptinezumab demonstrated statistically significant and clinically meaningful differences in reducing migraine frequency over the 12-week treatment period.

In Saudi Arabia, the prevalence of migraines is reportedly high, as indicated by published evidence (Figure 2). Current medications for migraine management in the Saudi population appear to be less effective than Eptinezumab. Presently, Onabotulinumtoxin A is emerging as the most promising novel treatment for migraines in Saudi Arabia, although studies on its effectiveness are limited. Introducing Eptinezumab to the Saudi market could potentially alleviate both the health impact of migraines on patients and the economic burden on the government. The involvement of major medical centers in Saudi Arabia in conducting clinical studies on Eptinezumab for migraine management could be a crucial step toward gaining approval for the drug's use in the country. This move may improve the therapeutic landscape for migraine sufferers in Saudi Arabia.



**Figure 2A:** showing the prevalence of migraines worldwide. Saudi Arabia population tends to be the highest among the world, who suffer from migraines by 30.3%. India and Kuwait seem to be similar by 28% and 27.9%, respectively. In contrast, USA and UK populations are the lowest among the world in getting migraine by 1.3% and 1%, respectively.

**Figure 2B:** showing the prevalence of migraines in Saudi Arabia. Taif city tends to be the highest among Saudi cities by 78.5%. Hail and Qassim province were similar by 32.1% and 30.7%, respectively. Dammam was the lowest among Saudi cities by 5.2%.

### Strengths and limitations

In this manuscript, we analyze the efficacy of Eptinezumab in preventing migraines, based on a meta-analysis of clinical trials conducted in different population. Despite potential variability and publication bias, our results indicate that Eptinezumab could significantly reduce migraine frequency and severity. We explore its implications for migraine management and call for further research to confirm these findings.

### Conclusion

This analysis evaluated Eptinezumab's efficacy in CM prevention in adults via two clinical trials. IV Eptinezumab, every 12 weeks, significantly reduced MMDs by -7.7 days with 100mg and -8.2 days with 300mg. Patients also experienced improved daily life and condition perception. With minor side effects, Eptinezumab was safe. Considering high migraine rates in Saudi Arabia and

limited treatment options, the authors recommend that the Saudi FDA explore eptinezumab's potential through local clinical studies.

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#### Authors' Contribution

-Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: all authors.

-Drafting the work or reviewing it critically for important intellectual content: all authors.

-Final approval of the version to be published: all authors.

-Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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