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Review Article

# COMPARISON OF EFFICACY AND SAFETY OF NEWER DRUGS APPROVED FOR THE TREATMENT OF MIGRAINE DISORDER: A REVIEW

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**ABSTRACT**

Migraine is a recurrent throbbing or pulsing headache with moderate to severe pain intensity. The pain is often one side of the head with nausea and weakness symptoms. Around 12 percent of Americans, 9 percent of Asians experiences migraine and the prevalence is highest among South Koreans (22.3%). The outcome of chronic migraine treatment can be quite disheartening, causing patients to feel out of options who have tried multiple treatments with no results. Poor efficacy, tolerability and safety of migraine preventive therapy in clinical practice lead to poor compliance and failure of therapy. The mean change in number or frequency of headache is considered as the outcome measure of migraine prevention therapy. Upon comparing all migraine prevention therapy, the Fremanezumab, Eptinezumab, Galcanezumab and Erenumab were considered as the front runner in controlling the severity and frequency of migraine. Among these drugs, Erenumab was most effective in controlling the frequency of migraine episodes as it produces more than 50 percent reduction in the mean number of monthly migraine days (MMD) over week 9-week 12. In addition to drug therapy, adequate rest, balanced diet, yoga and meditation will help patients to get rid of migraine severity. A multi-dimensional approach is essential for better control over migraine symptoms.

**Keywords:** Headache, Migraineurs, Nausea, Safety, Tolerability, Phonophobia


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## INTRODUCTION

Migraine is an extremely usual, persistent, and normally genetically-related neurovascular disorder which occurs at irregular intervals [1]. It is a weakening brain disorder impacting approximately fifteen percent of the world population. Generally, migraine attacks comprise of severe headaches which accompany by a group of symptoms, lasting for four to seventy-two hours, for instance, nausea, vomiting, photo-and phonophobia [2]. As a major cause of neurological disability worldwide and due to its nature, it is undoubtedly having a significant effect on society [3-5]. In addition, migraine can be categorized into episodic migraine and chronic migraine. The most common form of migraine is episodic migraine, has an attack of headache happening for less than 15 d monthly [3]. As a multifactorial genetic disorder, migraine has two mechanisms, which are the neuronal and vascular pathway that includes several dozens of gene variants with minimal effect size [4]. There are around twenty to thirty percent of migraineurs are affected by short-term focal neurologic symptoms, which can occur before or during the headache and it is called aura [5]. The frequency, duration, and intensity of the migraine attack can be different among individuals. The occurrence of temporary disability due to migraine attack creates a significant impact to the migraine patients' work and activities lead to impairment in productivity and quality of life of the patients [1].

The data extracted for this review is mainly on the antimigraine drugs used in the treatment of various migraine disorders. The main source of data used is PubMed, Nvivo, Mendeley, Evernote, CiteUlike, Biohunter, Delvehealth, Scicurve, and Google Scholar, etc. Articles on complementary therapy on migraine disorder and animal studies were excluded. The antimigraine drugs included in our studies are those that were approved by US-FDA, as according to Centre Watch. All the authors independently extracted the relevant information from studies that fulfilled our inclusion criteria and any disagreements were resolved with consensus. The information extracted included the trial phase, region, conditions of subjects and the outcome measures. This information was gathered and summarized into paragraphs, introducing each antimigraine drug comprehensively.

### Epidemiology

As a neurovascular disease, migraine is currently being considered as a severe and prevalent health issue. To be more precise, it has become the sixth-leading cause disability globally and the third-leading cause of disability in people of age less than 50-year-old [6-9].

Migraine has affected different populations, with the highest incidence in Europe and North America (13%), followed by Asia (9%) [10]. Besides, it has been shown through a recent study regarding the headache disorders in India, which outlined individuals suffering from various headaches, of which 26% of them suffer from migraine [11]. Furthermore, the 2010 Global Burden of Disease Study had presented that the worldwide prevalence of migraine was 14.7%, which was slightly lower as compared to the incidence of tension-type headache (20.1%) [12-14]. In 2013, the same study was being conducted and revealed that neurological disorders had contributed to over half of all years lost to disability [10-16]. In 2015, the study reported that migraine was considered one of the eight chronic diseases which influenced more than 10% of the global population [17]. Gender wise, it had a greater impact on women compared to men, with prevalence of 17% and 6% respectively, resulting to a remarkable socioeconomic burden to the society. Migraine was then proved to be the second-highest cause of years lived with disability globally in the 2016 Global Burden of Disease study [18].

Migraine also related to the people's socioeconomic burden, with respect to both standard of living and lost efficacy [19]. This is supported by previous studies, which indicated that about 9 out of 10 migraine patients are functionally affected during an attack, approximately half of them are gravely impaired and in need of bed rest. It has also been reported that those with migraine are only about half as productive at work compared to those without [8, 20]. Furthermore, the burden of migraine is higher in part-timers or those who are jobless, has low socioeconomic status, and no government insurance. These populations are presumably to have limited access to health care and treatment for their headaches. In addition, these people are more likely to be exposed to triggers and other factors that can aggravate headache. Therefore, this is progressively relevant as the managements of migraine and other severe headaches move from symptom-based, non-specific therapies to more specific, individualized, and cost-effective treatments such as the new anti-calcitonin gene-related peptide (anti-CGRP) antibodies. It is crucial to understand the distribution of headache in specific segments of the population as this allows the treatments to be accessible to those most in need [21]. The current conventional drugs control the severity of migraine at a certain level; however, no complete salvage from the recurrent migraine attacks. A novel antimigraine therapy is needed to control the severity and recurrent attacks, and also has the least side-effects. Hence, a review was carried out to compare the mechanism, efficacy and safety of antimigraine drugs that indicated for the treatment of migraine disorder.

**Management**

Migraine is generally managed with a different class of drugs, namely non-steroidal anti-inflammatory drugs (NSAID), 5-hydroxy tryptamine (5HT)-agonists, ergot preparations, and specific drugs targeting the receptors. Prophylactic treatment choices for migraines include drugs developed for diseases other than migraines such as depression, epilepsy and hypertension [22]. In the past ten years, inhibiting CGRP has appeared to be a possible mechanism to prevent migraine attacks. This is supported by recent evidence suggesting that dysfunctional activation of the trigeminovascular system involving CGRP is implied in migraine pathogenesis [22-25]. The drugs which are commonly used in migraine are discussed comprehensively below emphasizing their mechanism of action, efficacy and safety in migraine prevention or control. The summary of the efficacy and safety of newer drugs that recently approved for the treatment of migraine are compared and presented in table 1.

**Table 1: Comparison of efficacy and safety of newer drugs that approved by US-FDA for the treatment of migraine disorder**

| Author name | Title of the article | Study design | Outcome | Efficacy | Safety |
|---|---|---|---|---|---|
| **CGRP antagonist** | | | | | |
| **1. Fremanezumab** | | | | | |
| Dodick *et al.*, [49] | Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized clinical trial | Randomized, double-blinded, placebo-controlled, phase 3 study | Mean change from baseline in the mean number of monthly migraine days during the 12-week period after the first dose | 1.3-to 1.5-day reduction in the mean number of monthly migraine days over a 12-week period | Injection site-related pain |
| Bigal *et al.*, [50] | Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of chronic migraine: A multicentre, randomised, double-blind, placebo-controlled, phase 2b study | Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group phase 2b study | Mean change in the number of headache-hours | 675/225 mg group: –59·84 h<br>900 mg group: –67·51 h | Injection site-related pain |
| Cohen *et al.*, [51] | Fremanezumab as an add-on treatment for patients treated with other migraine preventive medicines | Randomized Placebo-controlled studies | Mean change in migraine days | Total reduction in migraine days for the duration of the study was 12.4 | Injection site-related pain |
| **2. Eptinezumab** | | | | | |
| Dodick *et al.*, [52] | Safety and efficacy of ALD 403 for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial | Randomised, double blind, placebo-controlled, exploratory, proof-of-concept phase 2 trial of an intravenous dose of ALD 403 at 26 centres in the USA | Frequency of migraine days | Week 1-4:-1.7 MHDs<br>Week 5-8:-1.0 MHDs<br>Week 9-12:-1.0 MHDs | 43 (52%) of 82 patients in the placebo group and 46 (57%) of 81 in the ALD403 group experience adverse events. Patients who received ALD403 had pyelonephritis; One patient had four serious adverse events, which are chest pain, transient ischaemic attack, conversion disorder, and dyspnoea. |
| Dodick, *et al.*, [53] | Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial | Single-dose, placebo-controlled study, exploratory phase 2 trial | Frequent migraine episodes | MHD at 5-8 w: Active (-5.6 MHDs) vs placebo (-4.6 MHlanfDs) | Mild to moderate adverse events occurred in 57% of patients in the eptinezumab group and 52% in the placebo group. 6 patients in the placebo group vs 7 patients in the eptinezumab group experience upper respiratory tract;<br>4 patients vs 1 patient experience urinary tract infections; fatigue (3 vs3), |

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| | | | | | back pain (4 vs 3), arthralgia (4 vs 1), and nausea (2 vs 3). No infusion reactions were reported 2 patients in the eptinezumab group and 1 patient in the placebo group experience serious adverse events. |
| **3. Galcanezumab** | | | | | |
| Forderreuther *et al*., [58] | Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies | Randomized, double-blinded, placebo-controlled, phase 3 study | Mean monthly migraine headache days (MHDs) | At month 1, 20% of patients had a sustained response of ≥50% reduction of MHDs over 6 months; about 41% of patients maintained ≥50% response over ≥3 months | Injection site-related pain |
| Skljarevski *et al.*, [57] | Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial | Randomized, double-blinded, placebo-controlled, multicenter, phase 3 study at 109 study centres in 11 countries | Mean monthly migraine headache days (MHDs) | 120 mg: -4.3 MHDs<br>240 mg: -4.2 MHDs | Injection site-related pain |
| Skljarevski *et al.*, [68] | Effect of Different Doses of Galcanezumab vs Placebo for Episodic Migraine Prevention A Randomized Clinical Trial | Randomized, double-blinded, placebo-controlled, phase 2b study in clinics of 37 licensed physicians with a specialty | Frequency of migraine headache days (MHDs) | 120 mg: −4.8 MHDs | Injection site-related pain |
| **CGRP-Receptor Antagonist** | | | | | |
| **1. Erenumab** | | | | | |
| Dodick *et al.*, [59] | ARISE: A Phase 3 randomized trial of erenumab for episodic migraine | Randomized, multicenter, double-blind, placebo-controlled, phase 3 study<br>Criteria: 577 participants with episodic migraine (EM), had 4-15 MMD with or without aura for at least 12 mo before the study | Change in monthly migraine days (MMD) over Month 3 of study. | 70 mg SC monthly vs placebo ($p<0.001$)<br>-2.9 d change in MMD from baseline | Most common AE-Upper respiratory tract infection |
| Reuter *et al.*, [62] | Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomized, double-blind, placebo-controlled, phase 3b study (LIBERTY) | Randomized, multicenter, double-blind, placebo-controlled, phase 3b study<br>Criteria: 246 participants with a history of EM with or without aura for at least 12 mo, had migraine for average of 4-14 d per months over 3 mo before the screening, had unsuccessful treatment with between two-to-four preventive treatments. | ≥50% reduction in the mean number of MMD over Week 9-Week 12. | 40 mg (via two divided 70 mg injections) SC monthly vs placebo 36/119 of erenumab group had ≥50% reduction in mean number of MMD vs 17/124 of placebo group had ≥50% reduction in mean number of MMD | Most common AE–pain at the injection site |
| Goadsby *et al.*, [61] | A Controlled Trial of Erenumab for Episodic Migraine (STRIVE) | Randomized, multicenter, double-blind, placebo-controlled, phase 3 study<br>Criteria: 955 | Change in the mean number of MMD over Month 4–Month 6 | 70 mg SC monthly, 140 mg SC monthly vs placebo ($p<0.001$ for each dose vs placebo)<br>70 mg shows-3.2 d | Most common AE-Nasopharyngitis |

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| | | participants with a history of migraine with or without aura for at least 12 mo prior to screening, had at least 4-15 migraine days per months and<15 headache days per month on average over 3 mo before the screening, demonstrated at least 80% adherence to reporting with an electronic diary in baseline phase | | change in MMD<br>140 mg shows-3.7 d change in MMD | |
| Tepper *et al.*, [63] | Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomized, double-blind, placebo-controlled phase 2 trial | Randomized, multicenter, double-blind, placebo-controlled, phase 2 study<br>Criteria: 667 participants with a history of chronic migraine, had 15 or more headache days per month, of which 8 or more of those days were migraine days, demonstrated at least 80% adherence to reporting with an electronic diary in baseline phase | Change in MMD in week 9-week 12 | 70 mg SC monthly, 140 mg SC monthly vs placebo ($p<0.0001$)<br>Both 70 mg and 140 mg shows-6.6 d change in MMD | Most common AEs: Injection-site pain, muscle spasm |

**Mechanism of action**

**a) Non-steroidal anti-inflammatory drugs**

Acetaminophen and NSAIDs which possess analgesic and anti-inflammatory actions in migraine by inhibiting the enzyme cyclooxygenase (COX) to reduce prostaglandin synthesis from arachidonic acid [26]. There are two cyclooxygenase enzymes which are COX-1 is widely expressed in gastrointestinal tract, whereas COX-2 is widely predominated at sites of inflammation [27]. Aspirin inactivates COX-1 irreversibly and inhibit the production of prostaglandin ($PGH_2$) where it acts as a primary precursor of thromboxane $A_2$. Aspirin interacts with the amino acid Arg120 which result obstructing of the accessibility of arachidonic acid to the Tyr385 hydrophobic channel at catalytic site [28].

**b) 5-hydroxy tryptamine (5HT)-agonist**

In the 1990s, the emergence of the selective 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors agonists was a significant advancement for the acute management of migraine. Triptans exhibit antimigraine effects through cranial vasoconstriction and by inhibition of CGRP in the perivascular nerve terminals, subsequently reducing the activation of trigeminal nociceptors [29-31]. A few examples of the triptans include zolmitriptan, rizatriptan, and naratriptan.

**c) Ergots**

According to the vascular theories of migraine, the ergot alkaloids as vasoconstrictors were turned into one of the earliest approaches towards migraine attacks [32]. Antimigraine drugs introduced to the market were ergotamine (E) tartrate as the first pure ergot alkaloid and dihydroergotamine (DHE) [33]. Ergots are indicated for migraines that also present with a long period and infrequent headaches and to patients who are likely to adhere with dosing restrictions. E and DHE once remained as the only available acute specific antimigraine treatments until sumatriptans were developed in 1980s. The ergots have high selectivity for various receptors, such as dopamine, noradrenaline and serotonin (5-hydroxytryptamine). E and DHE interact with 5-$HT_{1A, 1B, 1D, 1F, 2A, 2C, 3, 4}$ subtypes.

**d) Others drugs**

Botulinum toxin A (BoNT-A), due to its healing properties and its ability to alleviate pain, an increasing number of studies have been carried out for the past ten years to investigate the efficiency of BoNT-A in treating migraines. Animal and human studies have revealed that BoNT-A inhibits the release of the neurotransmitters glutamate A, calcitonin gene-related peptide and Substance-P, which are important mediators of inflammatory pain. Hence, nociceptive signals reaching the central system are minimized. BoNT-A is administered peripherally in the form of injections to the head or neck [32].

**Specific management**

The specific management of migraine includes CGRP antagonists and its receptor antagonists, both are considered simultaneously in some cases depends on the severity of the condition.

**Calcitonin gene-related peptide antagonists**

**a) Fremanezumab**

Fremanezumab, also known as Ajovy is the second drug after erenumab (Aimovig) to be approved by the FDA for the preventive treatment of migraines. Engineered by recombinant DNA technology, Fremanezumab is a fully-humanized monoclonal antibody. It has a strong affinity for CGRP ligand, a neuropeptide that is strongly implicated in migraine pathophysiology. This antibody is made up of 1324 amino acids and has a molecular weight of approximately 148 kDa. Being highly specific, tolerable and safe,

Fremanezumab has proved to be an ideal drug development for migraines. Goadsby *et al.*, found direct evidence that the prophylactic effect of CGRP-mAbs is achieved mainly through their ability to prevent the activation of peripheral trigeminovascular neurons of the Aδ type by events that lead to cerebral release of CGRP during a migraine headache [34, 35]. While erenumab blocks CGRP receptor, fremanezumab binds to the CGRP molecule and blocks its attachment to the CGRP receptor. Fremanezumab has an estimated half-life of approximately 31 d. Two subcutaneous dosing options of Ajovy exist which are a monthly dose of 225 mg or 675 mg to be administered every 3 mo. In clinical trials, hypersensitivity reactions including rash and pruritus were reported at injection sites within hours to one month after administration.

**b) Eptinezumab**

Eptinezumab, ALD403 is a fully-humanized IgG1 antibody that binds specifically and selectively to both alpha and beta forms of the human CGRP. ALD403 also binds potently (Kd<20 pM) to human CGRP [36].

**c) Galcanezumab**

One of the recently approved drugs for migraine prevention called galcanezumab-gnlm, also known as LY2951742, is an entirely humanized monoclonal antibody which potently and selectively binds to CGRP ligand and blocks its binding to the receptor, hindering CGRP-mediated vasodilation effects [36, 37].

**Calcitonin gene-related peptide receptor antagonists**

**a) Erenumab**

Erenumab is the first FDA-approved GCRP-receptor monoclonal antibody specifically developed for the management of migraines [38]. It is formerly known as AMG334, due to its nature as a fully human monoclonal antibody, it specifically attaches to CGRP receptor. Attachment sites of this receptor is closely related to receptor activity-modifying protein 1 (RAMP1) complex and calcitonin receptor-like receptor (CLR). Through this binding, the biological activities of CGRP are blocked with an IC50 (2.3±0.9 nM) [39]. Erenumab is 5000-fold more specific for CGRP receptor as compared to any other human calcitonin family receptors. Erenumab is considered as a very large molecule where its molecular weight is about 150.000 kDA. In the contrary, small molecule of CGRP receptor antagonists have molecular weight of less than 500 kDA, making it possible to enter the central nervous system (CNS) [40]. Due to its large molecular size, it poses a low risk of penetration into the blood-brain barrier (BBB) that can result in adverse reactions associated with CNS. According to Eftekhari *et al.*, [41] erenumab has mode of action outside of BBB, specifically at trigeminal ganglion. Site of expression of CGRP are in neurons of greater sizes, specifically Aδ neurons as well as the cells of satellite glial. Meanwhile, CGRP receptors are dispersed in c-fiber neurons of relatively smaller diameter. Inhibitory action of erenumab on activation of Aδ results in the preventive effect in migraines. Erenumab possess half-life of 26 d, and this explains the need for drug administration to be done only once a month [42]. Route of administration of this drug is through subcutaneous injection thus having its primary metabolism handled by the reticuloendothelial system. It is found that erenumab is not eliminated via hepatic, renal or biliary process, which lowers the risk of drug-drug interactions by not competing with other drugs via these excretion pathways. Through various studies, erenumab is considered to be highly potent in inhibiting the capsaicin-induced dermal blood flow (CIDBF) [38].

**Efficacy**

The efficacy of recently marketed antimigraine drugs was critically analyzed using the reduction in pain intensity and the number of headache-free days. The details are presented below.

**a) Non-steroidal anti-inflammatory drugs**

Aspirin is well-known in the treatment of migraine. A systematic Cochrane review discovered that a single dose of 1g of aspirin relieves headache in 52% of attacks and 32% for placebo at 2 h, whereas 24% shown free of pain at 2 h compared to 11% for placebo. At a dose of 1g acetaminophen alone had high efficiency while at a dose of 650 mg, acetaminophen was not better than placebo [27]. Acetaminophen, other NSAIDs and aspirin are the most widely used drugs for migraine attack. Nonetheless, many randomized controlled trails proved that the efficacy of acetaminophen is slightly lower than other NSAIDs for a migraine attack.

**b) 5-hydroxy tryptamine (5HT)-agonists**

Oral sumatriptan 50 mg and eletriptan 40 mg are the most advantageous as a first-line specific acute migraine therapy, while subcutaneous sumatriptan 6 mg is the most effective currently marketed drug [43]. Zolmitriptan has an efficacy of 62% at 2 h and up to 78% within 4 h on a regular dose 2.5 to 5 mg orally or as intranasal spray. One of the new delivery methods for an aged acute migraine therapy is Zecuity® which is a battery-powered, transdermal sumatriptan patch considered more suitable for migraine headaches and cluster headaches [44].

**c) Ergots**

Oral formulations of ergot are poorly absorbed due to extensive first-pass metabolism with nausea as its main side effect, while its rectal form shows higher efficacy where relatively higher plasma levels are observed. Rectal formulation of ergot is thus recommended for patients with early onset of migraine with severe nausea and vomiting. DHE are currently available as intravenous, intramuscular, subcutaneous and intranasal formulations. Among ergot alkaloids, DHE is at an advantage as it is marketed with various administration possibilities, is relatively a weaker vasoconstrictor [45] and has longer half-life. Due to its longer half-life, it has a low risk of medication overuse [46] as well as lesser side effects. Usage of ergots as antimigraine should be limited only to younger patients who respond poorly to other treatments [47].

**d) Others drugs**

Similar to other preventive migraine treatments, it has been found that the advantageous effects of BoNT-A could be noticed mostly in 2nd and 3rd months of post-treatment period. This is in accordance with findings which state that it takes up to 3 w for botulinum toxin to achieve its maximum efficiency. In patients suffering from chronic migraine, it can be noted that BoNT-A reduces the number of migraine days by 2 d over a period of one month. Due to the unavailability of high-quality evidence, it remains unclear as to whether BoNT-A is effective in preventing episodic migraine [48].

**Specific management**

**Calcitonin gene-related peptide antagonists**

**a) Fremanezumab**

Dodick *et al.*, enrolled 875 participants in a phase 3, double-blind, placebo-controlled, parallel group study whereby fremanezumab was administered either monthly or a higher dose was given only once while others received placebo. The primary end point being investigated in this study was the mean change from baseline in the mean number of MMD, 12 w after the first injection. Based on the findings, 12 w after receiving the first dose, a reduction from 8.9 to 4.9 MMD was observed for the monthly fremanezumab dosing group. Patients received a single higher dose of fremanezumab showed a 9.2 to 5.3 MMD reduction while placebo group showed a decrease from 9.1 to 6.5 d. The MMD declined by at least half in 47.7% of patients who were injected with fremanezumab monthly and 44.4% those who received the single higher dose of fremanezumab as compared with 27.9% for the placebo group. This study also concluded that among patients with episodic migraine, subcutaneous fremanezumab reduced the MMD by 1.3 to 1.5 d [49]. In another phase 2b, double-blind, double-dummy, placebo-controlled, parallel-group study conducted by Bigal *et al.*, participants were enrolled to receive 675/225 mg fremanezumab, 900 mg fremanezumab or placebo. During weeks 9–12, findings showed that in the 675/225 mg group, the mean change from baseline in the number of headache-hours was −59·84 while in the 900 mg group, the change was −67·51 h and −37·10 h in the placebo group. A 38% decrease in the headache-hours was observed for those who received 675/225 mg dose of fremanezumab, while in

the 900 mg group, headache-hours decreased by 43% compared to only 22% in the placebo group [50]. In two randomized placebo-controlled studies carried by Cohen *et al.*, the total decline in migraine days was 12.4 for fremanezumab and 7.4 for placebo during the study period, in patients who were already on other migraine preventive medications. Decreases in moderate/severe headache days were also observed. Similarly, the number of days where acute medication was used for headaches decreased compared to placebo. The study concluded that in patients who were already on anti-migraine therapy, fremanezumab significantly reduced the MMD as well as moderate to severe headache days, and days whereby acute medication was used. Hence, the efficacy of fremanezumab as a complementary therapy to other migraine preventive medications was hence validated by this study [51].

**b) Eptinezumab**

Dodick *et al.*, in their randomized, double-blind, placebo-controlled, exploratory phase 2 trial in migraine patient population stated due to its momentary and mild or moderate-severe adverse effects, Eptinezumab (ALD403) was normally safe and well-tolerated. On week 5-8, the average number of days with migraine reduced compared to initial number. In addition, 75% of the patients treated with ALD403 experienced a decrease of 50% of migraine days, whereas another 44% undergone a decrease of 75% at this same time point. Moreover, 16% of the patients in ALD403 indicated in a post-hoc analysis do not have any migraine attacks in which there's a 100% decline in day of migraine in the entire study period of twelve weeks. Nonetheless, placebo group do not show fully decline in migraine days if compared to treatment group [52]. Dodick *et al.*, [53] in a single-dose and placebo-controlled study demonstrated patients with frequent migraine attacks received single dose of eptinezumab by intravenous route; where 163 participants aged between 18 and 55 y old with 5 to 14 migraine were randomly assigned to receive either 1 gm eptinezumab or placebo intravenously every 28 d for up to 24 w. In which, 57% of the patients from the treatment group experienced mild to moderate adverse effects compared to placebo group. Generally, the adverse effects were arthralgia, nausea, upper respiratory tract infections, fatigue, urinary tract infections, back pain.

Seven patients from the treatment group and 6 patients from placebo experienced upper respiratory tract infections; whereas only 1 patient from ALD403 group and 4 patients from placebo had urinary tract infections and arthralgia. There is an equal number (n=3) of patients from both group noted with from fatigue, 4 and 2 patients experienced back pain and nausea respectively. There were 2 patients from ALD403 and 1 patient from placebo group experienced serious adverse effects. It is undeniable that higher response rates showed in ALD403 group with approximately 20% higher than placebo. Furthermore, 16% of patients were reported to have no migraine days when treated with eptinezumab [54].

**c) Galcanezumab**

Schuster *et al.*, in their phase two randomized, controlled trial involving 218 participants with episodic migraine, each participant received a subcutaneous 150 mg dose of galcanezumab or a placebo every fortnight [55]. The primary endpoint of reduction in monthly migraine headache days (MHDs) was achieved during the third month of therapy with a monthly decrease of 4.2 and 3.0 MHDs in the treatment and placebo group, respectively. The 100% responder rate, defined as absence of migraine attacks during the 3-month trial, was also lower in the controlled group than in the treatment group [55]. A study by Camporeale *et al.*, compared the efficacy of 120 mg and 240 mg of galcanezumab, and reported that the overall mean reduction in MHDs over 12 mo were 5.6 for 120 mg and 6.5 for 240 mg. Additionally, the improved functioning level was observed, and headache-related dysfunction was reduced in both dose groups [56]. Subsequently, Skjarevski *et al.*, in their randomized, double-blinded, placebo-controlled, multicenter, phase 3 study at 109 centers in 11 countries found a reduced mean monthly MHDs of 4.3 and 4.2 for 120 mg and 240 mg of galcanezumab, respectively [57]. The most recent finding was from a phase 3 study conducted by Forderreuther *et al.*, whereby 20% of the patients had a sustained response of equal or more than 50% reduction of MHDs over six months. Among the 20%, 41% of them maintained the said response for three months or more [58].

**Calcitonin gene-related peptide receptor antagonists**

**a) Erenumab**

ARISE [59] was a phase 3 study conducted over 3 mo, in which the monthly subcutaneous injections of 70 mg of erenumab vs placebo were studied in 577 episodic migraine (EM) patients, and the change in MMD as primary outcome was assessed in month 3 of the treatment phase. In regards to this end-point, erenumab showed more promising results relative to placebo where it showed-2.9 d change of MMD from its baseline while placebo group showed-1.8days change of MMD. This further supports an earlier consideration that 70 mg is the minimal effective dose in patients with EM [60]. In STRIVE [61], of the same study design as the previous trial, 70 mg and 140 mg of erenumab were used. Results showed a reduction in MMD of 3.0 d in patients with 70 mg, and 3.5 d' reduction with 140 mg, whereas 1.7 d' reduction in MMD was observed in placebo group. Erenumab at both doses elicited a change in MMD that was significantly higher by almost 2 d compared to placebo. The efficacy of 140 mg Erenumab was higher compared to 70 mg and placebo regarding all endpoints. In another phase 3b study LIBERTY [62], patients whose previous preventive treatments were unsuccessful in EM, and administered with either placebo or 140 mg of erenumab given in two subcutaneous injections of 70 mg/1 ml. At week 12, among 119 patients who received erenumab, 30% of them showed ≥50% decline in the mean number of MMD. Meanwhile, in placebo group consisting of 124 patients, only 14% showed the same result. Additionally, through weeks 0-4 and weeks 5-8, relative to placebo group, higher proportion of the erenumab group had ≥50% decrease in mean number of MMD. For secondary endpoints, erenumab group showed a reduced MMD specifically by 1.8 d. while placebo reduced 0.2 d in MMD. This further proves erenumab as an alternative therapeutic agent in EM patients whom other traditional preventive treatments are contraindicated, unsuccessful or poorly tolerated.

In addition to that, another phase 2 trial [63] demonstrated the efficacy of treatment with erenumab given in 667 patients suffering from chronic migraines. Patients were assigned with either monthly subcutaneous placebo, 70 mg or 140 mg of erenumab. Patients receiving 70 mg or 140 mg of erenumab demonstrated a significant change in MMD of-6.6days for both dose vs placebo at–4.2days. Besides, 40% of a group of 188 patients treated with 70 mg erenumab and 41% of 187 patients given 140 mg erenumab obtained ≥50% reduction in mean number of MMD as compared to 23% of 281 patients in placebo. Erenumab shows promising efficacy in prevention of both chronic as well as EM through various demonstrations in both phase 2 and 3 trials.

**Safety**

The safety profiles of conventional antimigraine drugs are compared with specific drugs that are exclusively used to block or antagonize the receptors. The safety profiles of all old drugs are also compared with recently marketed drugs that are used for the treatment of any form of migraine. The details are presented here.

**a) Non-steroidal anti-inflammatory drugs**

NSAIDS are known to have gastrointestinal side effects, including peptic ulcer, increased risk of myocardial infarction and heart failure. The incidence of side effects was proportional to dose [27].

**b) 5-hydroxy tryptamine (5HT)-agonists**

Triptans are known to have fewer side effects than ergot alkaloids. However, cardiovascular disease, which include uncontrolled hypertension is a contraindicated factor because triptans also vasoconstricts the coronary arteries [29].

**c) Ergots**

Clinical effect of ergots is due to their agonist activity primarily at 5-$HT^{1B/D}$ receptors and then 5-$HT^{1F}$ receptors to a lesser extent [64]. This polypharmacology is believed to contribute to its adverse reactions. Side effects of ergots are reflected on their agonism on 5-$HT^{1A}$ receptors in which nausea and dysphoria are involved and at 5-$HT^{2A}$ receptors that leads to peripheral vasoconstriction. Side effects of ergots on cardiovascular activity is then related to its vasoconstrictive

actions [32]. Ergots also act on dopamine D2 receptors, presenting nausea and vomiting in patients receiving this treatment [64]. Despite its inexpensiveness, ergots are associated with tolerability problems, potentials of vasoconstriction, poor bioavailability of its oral formulations, and risk of medication overuse, and its clinical use is relatively less extensive nowadays [33].

**d) Others drugs: (Botulinum toxin A)**

Most of the studies conducted have shown that Botulinum Toxin A is well tolerated by migraine sufferers, with patients exhibiting a significantly higher rate of treatment-related adverse effects when larger doses of BoNT/A are administered [48].

**Specific management**

**Calcitonin gene-related peptide antagonists**

**a) Fremanezumab**

In a study conducted by Dodick *et al.*, at least one adverse event was reported by 66% of the participants who were injected with fremanezumab monthly at a higher dose compared to 8% who were given placebo. The adverse event profile of fremanezumab in this trial matches with previously conducted clinical trials, whereby no clinically significant patterns of serious adverse events are observed [49]. In another phase 2b, double-blind, placebo-controlled, parallel-group study conducted by Bigal *et al.*, adverse events were reported by 40% of patients in the placebo group, 53% of patients who received 675/225 mg dose of fremanezumab and 47% of those who received 900 mg fremanezumab. The most common adverse events experienced were mild injection-site pain and pruritus [50]. Cohen *et al.*, conducted two randomized placebo-controlled studies on various subcutaneous doses of fremanezumab versus placebo as an add-on-therapy in episodic migraine and chronic migraine for a period of one month. Treatment-emergent adverse events were reported by 44% of patients who received placebo and 55% of patients receiving any other migraine preventive drug. Serious adverse events were recorded in only 2% of patients receiving fremanezumab. It can be concluded that fremanezumab is well tolerated with no severe treatment-related adverse events and deemed safe for use in migraine sufferers [51].

**b) Eptinezumab**

A group of 174 patients in the USA assigned to receive either treatment (ALD403) or placebo group. Among this, 57% of the patients (n=81) in the treatment group and 52% (n=43) in the placebo group experienced adverse events. The most frequent adverse events were upper respiratory tract infection (URTI), urinary tract infection (UTI), fatigue, back pain, arthralgia and nausea and vomiting. Six patients from the placebo group and 7 patients from the treatment group affected with URTI. There was an equal proportion of patients suffering from UTI and arthralgia, which was 4:1 in both placebo and treatment group. Moreover, there was an equal percentage of patients suffering from fatigue in both the treatment and placebo group. A 4:3 ratio of the patients was having back pain; 2 and 4% of the patients experienced nausea and vomiting after receiving placebo and ALD403, respectively. There were four serious adverse effects observed in the treatment group, while only one adverse effect was noted in the placebo group. Nonetheless, among both treatment and placebo group, there was no reported significant difference between laboratory safety data or vital signs. A-5.6 MMD were reported in the treatment group and-4.6 MMD for placebo group on the average change in day of migraine between baseline and weeks five to eight [52].

**c) Galcanezumab**

A study by Schuster *et al.*, concluded that injection site reactions were more commonly observed in the group treated with galcanezumab than the control group. However, the treatment was well perceived without major adverse consequences [55]. In 2018, the safety and tolerability of galcanezumab were further investigated among 135 patients diagnosed with episodic or chronic migraine, and the findings revealed that most patients experienced treatment-emergent adverse effects (TEAE) include injection site reaction, nasopharyngitis, URTI, back pain and sinusitis [56].

**Calcitonin gene-related peptide receptor antagonists**

**a) Erenumab:**

A number of studies have been conducted appraising the safety profile of erenumab in the treatment of migraines. The ARISE [59] study with 70 mg erenumab reported URTI, whereas LIBERTY [62] study showed injection-site pain in its 140 mg intervention arm. Another study by Goadsby *et al.*, [61] reported nasopharyngitis as its most frequent adverse event (AE) in both 70 mg and 140 mg erenumab treatment groups. In a phase 2 study by Tepper *et al.*, [63] pain at the injection site was one of the most prominent AEs, occurring in 4% of each 70 mg and 140 mg erenumab groups, as well as muscle spasm in 4% of patients given with 140 mg erenumab. Two serious AEs; traumatic orbital fracture and one incident of migraine attack were reported in the group treated with erenumab; however, it was assumed that both cases had nothing to do with the active drug [62]. Other common AEs include constipation [59, 61], nasopharyngitis [61-63], fatigue and sinusitis were also observed. As erenumab is of human IgG2 antibody, possibilities in the development of neutralizing anti-drug antibodies (ADA) decreases [65]. In ARISE, at week 12, 12 out of 279 patients treated with erenumab were shown to develop anti-erenumab-binding antibodies (AB). At week 4, 1 of the 12 patients showed positive neutralizing AB, a, however negative result for the same AB in his subsequent visit [59]. Tepper *et al.*, [63] also confirmed that occurrence of binding AB in 6% patients of 70 mg group and 2% of 140 mg group, however, without neutralising AB. There was no relationship between this occurrence and AE in this study [63]. Incidence of anti-erenumab AB is rare and remit in most of studies. Apart from serum chemistry, no notable abnormalities and alterations were reported associated to primary vital signs, electrocardiogram (ECG) testing, and laboratory monitoring in all patients participating in all studies evaluated above [59, 63-65]. In a study, only one patient showed abnormal rise in alanine and aspartate aminotransferase at week 4 of study; the reading then returned to baseline in subsequent visit in week 8 [63]. As erenumab does not undergo hepatic metabolism, there were no significant impacts on liver enzymes, unlike the hepatotoxicity associated in treatment with telcagepant, a small molecule CGRP receptor antagonist [66, 67]. There were no deaths reported in studies conducted for erenumab [59, 61, 62]. The incidence of AEs in both erenumab and placebo interventions were similar [59, 61-65] and this further confirms the safety of the administration of erenumab. Erenumab is preferred as migraine preventive treatment with positive efficacy and safety profile, contributed by its pharmacokinetics [38].

**CONCLUSION**

All the existing antimigraine therapies were included for comparison of efficacy and safety in controlling repetitive migraine attack. Upon comparison, there are four migraine prevention drugs were considered more effective in terms of controlling the severity and frequency of migraine attack; there are Fremanezumab, Eptinezumab, Galcanezumab and Erenumab. Among these, Erenumab, a CGRP receptor antagonists at a dose of 70 and 140 mg was found to be most effective in controlling the frequency of migraine episodes. Erenumab may be a suitable alternative therapeutic agent in EM patients whom other traditional preventive treatments are contraindicated, unsuccessful or poorly tolerated as it produces more than 50 percent reduction in mean number of MMD in just few weeks of therapy.

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**CONFLICT OF INTERESTS**

Declared none

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