Migraine: Pharmacological treatments in 2022 & beyond

Executive Summary

Overview

Migraine is a complex headache disorder that affects 1.04 billion people globally, with a higher prevalence in women than men. It is characterized by frequent episodes of unilateral headache with pulsating pain. There are three types of migraine: migraine without aura, migraine with aura, and chronic migraine. Apart from headache, other common symptoms of migraine include photophobia, phonophobia, vomiting, and nausea.

Standard management strategies

The management of migraine includes acute and preventive treatment approaches. Acute medication is administered at the initiation of migraine when the pain is mild. Analgesics, non-steroidal anti-inflammatory drugs, and triptans are the standard medications for acute treatment.

Preventive treatment is given in the absence of headaches. This treatment aims to reduce the frequency and severity of headache attacks. Beta-blockers, angiotensin-II receptor blockers, and anticonvulsants are the standard preventive medications.

Limitations of standard medications

Standard medications are effective, but they have severe side effects, sub-optimal treatment response, and poor adherence. In addition, triptans are counter-indicative for people with or at risk of cardiovascular disease. These limitations have led to the development of new migraine therapies with a better safety profile.

Recent development in migraine therapy

Since 2018, the US-Food & Drug Administration (FDA) has approved Lasmiditan (a serotonin receptor agonist), trudesha (a drug delivery device for dihydroergotamine), monoclonal antibodies against calcitonin gene-related peptide (CGRP), and CGRP receptor antagonists. Current evidence suggests that these medications have better safety and tolerability profile than standard medications. The introduction of these medications

has broadened treatment options for patients for whom standard treatments are ineffective.

A 26-year-old woman, a migraine patient, experienced a headache during her travel to Europe. Her headache was triggered after hitting her head during a sledding accident, and it disappeared after several hours. After about ten days, she again experienced a severe headache in the bitemporal and occipital regions. And this time, the pain was associated with fatigue, nausea, and vomiting. About five days later, she developed stiffness in her neck accompanied by a persistent severe headache. She cut short her trip and returned to the USA[1].

Adapted from a case report from NEJM

Overview

Prevalence

According to the Global Burden of Disease (GBD) study, migraine is the second leading cause of disability globally. Migraine affects about 1.04 billion people worldwide, with age-standardized prevalence higher in women (18.9%) than men (9.8%)[2].

Socio-economic burden of migraine

Migraine affects the quality of life of an individual by causing unaccountable functional disability and reduced productivity.

In the GBD study published in 2016, researchers measured the burden of migraine in years lived with disability (YLDs). YLDs were calculated by multiplying the average time spent with headache and disability weight. According to the study, migraine caused 45.1 million YLDs globally. On average, a person with migraine spent 8.5% of a year in migraine-related disability. Compared to a healthy individual, an affected person experienced a health loss of 43.4% during a migraine attack. Migraine was more burdensome in females aged 15 to 49 with 20.3 million YLDs.

In a recent patient survey conducted in Canada, an annual economic cost per patient for chronic migraine was estimated to be $25,669, high-frequency episodic migraine was $24,885, and low-frequency episodic migraine was $15,651. Out of 287 patients who participated in a survey, 262 patients (91%) reported moderate to severe disability due to

headaches. Patients also reported activity impairment and reduced productivity due to migraine (Table1)[3].

Table 1 Work Productivity and Active impairment (WPAI) due to migraine	
Work time missed	20.6%
Overall work impairment	51%
Activity impairment	52.4%
Table adapted from Amoozegar F et al., Can J Neurol Sci. 2022;49(2):249-262	

What is migraine?

Migraine is a primary headache disorder characterized by recurrent headaches and is associated with nausea, vomiting, photophobia, and phonophobia. The headache is unilateral with moderate to severe pulsating pain. However, bilateral headache is also not uncommon. Migraine symptoms occur in three phases: prodromal, headache, and postdrome[4].

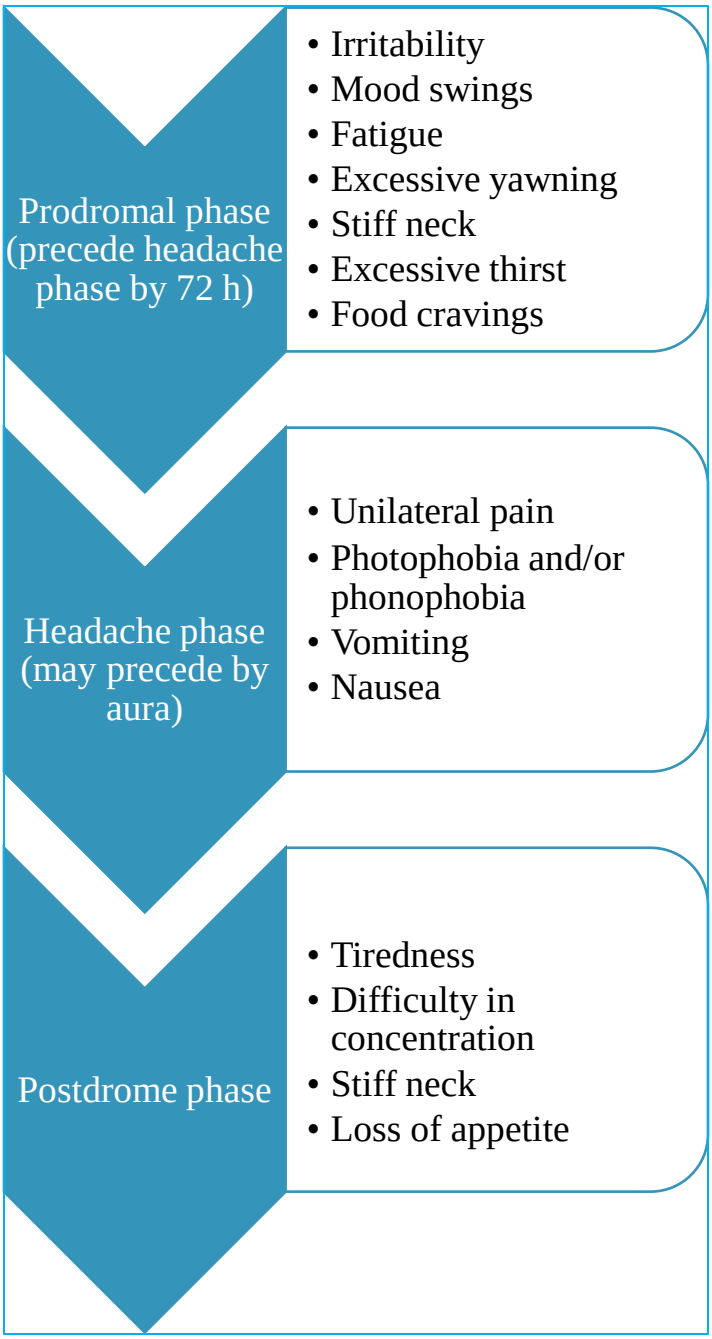

Prodromal phase (precede headache phase by 72 h)
• Irritability
• Mood swings
• Fatigue
• Excessive yawning
• Stiff neck
• Excessive thirst
• Food cravings
Headache phase (may precede by aura)
• Unilateral pain
• Photophobia and/or phonophobia
• Vomiting
• Nausea
Postdrome phase
• Tiredness
• Difficulty in concentration
• Stiff neck
• Loss of appetite

Table 2 Classification of migraine according to International Classification of Headache Disorders (ICHD-3)[5]	
Episodic migraine (EM) without aura	• Headache episodes occur fewer than 15 days per month • Headache is recurrent that lasts for 4-72hrs • Throbbing or pulsating unilateral pain of moderate to severe intensity • Headache is aggravated by routine physical activity, e.g., walking or climbing stairs
Episodic migraine with aura	• Aura occurs with every or some headache attacks • Aura manifests visually in the form of scotomas, tunnel vision, arc or band of absent vision with a bright zigzag border • Aura symptoms spread gradually over ≥ 5 min and can occur in succession. • Aura is mostly accompanied by headache within 60 mins. • Symptoms unique to this migraine are unilateral headache as pins and needles and/or numbness that spreads gradually in the face or arm • Other common symptoms include speech disturbance, vertigo, dysarthria, hemiplegia, repeated monocular visual disturbance
Chronic migraine (CM)	• Headache episodes occur for over 15 days per month for more than three months • Headache episodes occur with or without aura

Standard treatment strategies for migraine

The primary purpose of migraine treatment is to reduce severity and duration of the headaches and associated symptoms of photophobia and/or phonophobia. Migraine management includes two treatment approaches—acute and preventive.

Acute treatment is given at the onset of migraine pain when the pain is mild. The widely used acute treatments include:

- Over-the-counter (OTC) analgesics
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Triptans[6].

OTC analgesics & NSAIDs are the first line treatment for mild to moderate migraine. Most of these drugs inhibit cyclooxygenase, an enzyme involved in the production of prostaglandins—a promotor of inflammation. According to animal studies, inflammation activates the trigeminovascular system that in turn activates pain pathways and other central nervous system pathways causing migraine symptoms[7,8,9].

Naproxen sodium, acetylsalicylic acid, ibuprofen, and diclofenac potassium are the commonly prescribed NSAIDs[6]. Acetaminophen is the only OTC analgesic that has shown limited efficacy in migraine[10]. Opioid-based analgesics are generally not recommended because of their addiction potential.

Triptans are the second line of acute medications for moderate to severe migraine or when NSAIDs are ineffective in treating migraine. Triptans are selective serotonin, 5-HT1B/1D receptors agonists. The activation of the serotonin pathway inhibits the trigeminovascular system[8]. Sumatriptan, zomitriptan, almotriptan, froatriptan, naratriptan, eletriptan, and rizatriptan are the commonly prescribed triptans[6].

Preventive treatments are recommended for patients who experience two or more severe headache days per month despite taking acute medications. The aim of preventive treatment is to reduce the frequency and severity of migraine attacks (Table 3).

Table 3 Preventive treatment medications[11]	
1st line medication	• Beta-blockers (propranolol, bisoprolol) • Angiotensin II-receptor blocker (candesartan) • Anticonvulsant (topiramate)
2nd line medication	• Tricyclic antidepressant (amitriptyline) • Calcium antagonist (Flunarizine) • Anticonvulsant (sodium valporate[a])
3rd line medication	• Onabotulinumtoxin A

sodium valporate[a] not recommended for women of childbearing potential

Limitations of standard medications

Standard migraine medications effectively reduce migraine attacks and improve patients' quality of life. However, these medications are not effective in all patients. In addition, they have a poor adherence rate due to severe side effects. Acute medications produce gastrointestinal-related side effects (nausea, vomiting, and constipation) requiring a prescription of antiemetics. Triptans pose additional challenges:

1) Their vasoconstriction effects make them unsuitable for patients who have or are at risks of developing cardiovascular disease (CVD).

2) Their overuse increases the risk of developing medication-overuse headaches (MOH).

Recent development in migraine therapy

The past few years have seen the emergence of new therapeutic approaches for migraine. Various evidence indicates a better safety profile of new medications and

their efficacy for patients for whom standard medications are either ineffective or unsuitable.

Lasmiditan received FDA approval for acute treatment of migraine. Lasmiditan is a selective serotonin 5-HT1F receptor agonist. Unlike triptans, lasmiditan doesn't have vasoconstriction effects making it safe for patients who are at risk of developing CVD[12,13].

The safety and efficacy of lasmiditan were evaluated in randomized, double-blind, and placebo controlled clinical trials. At 2 hrs post-medication, patients were free of headache pain and most bothering symptoms (MBS) (nausea, photophobia and/or phonophobia) (Fig. 1 & 2).

Fig. 1 Pain free at 2hr

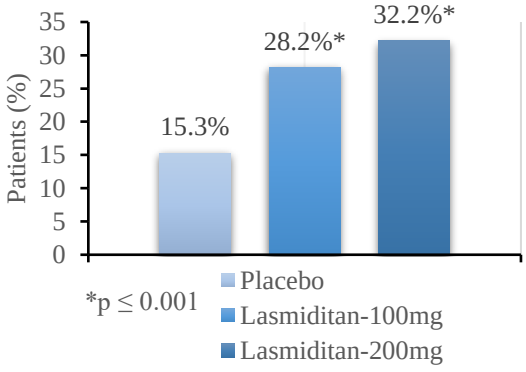
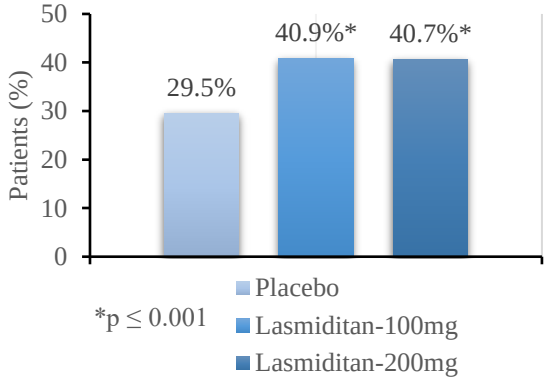


Fig. 2 MBS free at 2hr



Adapted from Kuca B et al., *Neurology*. 2018;91(24):e2222-e2232

The incidence of treatment-emergent cardiovascular events was low—five patients (out of 1230) experienced palpitations, and two experienced bradycardia[11]. Dizziness, fatigue, lethargy, nausea, burning or prickling sensation, and drowsiness were the most common treatment-emergent adverse events (TEAE) with mild or moderate intensity[12,13]. The frequency of TEAEs decreased during subsequent attacks. Less than 45% of patients experienced the same adverse event in subsequent attcks[12].

The major concern that can limit lasmiditan's use is the risk of developing serotonin syndrome that induces drowsiness. Therefore, after taking Lasmiditan, driving is not advisable for 8 hrs[11,13].

Trudesha (formerly INP104) is approved as acute treatment for migraine. Trudesha is a drug delivery device with a proprietary precision olfactory delivery technology that delivers dihydroergotamine mesylate (DHE) in the upper nasal space. DHE is an established acute migraine treatment; however, it requires intravenous administration for a better clinical efficacy making it unsuitable for at-home use[14]. Further, the delivery of DHE through nasal spray, oral inhalation, and intramascular or subcutaneous injections showed variability in bioavailability and clinical efficacy[15]. The new delivery technology of trudesha allows easy administration of DHE at home. In addition, the delivery of DHE to the upper nasal space increases its systemic absorption and bioavailability.

The safety, tolerability, and efficacy of trudesha were evaluated in a single-arm open-label clinical trial (STOP 301). Patients self-administered DHE using trudesha at the onset of migraine pain. 36.7% of patients reported INP104 related adverse events in the 24 week treatment period and 45.2% of patients in the 52 week treatment period (Table 4). No changes in the nasal mucosa were observed. At 2 hrs post-medication, 38% of patients experienced freedom from pain, and 52.1% experienced freedom from MBS[16].

Table 4 Common treatment-related AEs

Adverse events (AEs)	24-week N= 354 n (%)	52-weeks N = 73 n (%)
Nasal congestion	53 (15.0)	13 (17.8)
Nausea	24 (6.8)	5 (6.8)
Nasal discomfort	18 (5.1)	5 (6.8)
INP104 related abnormal taste	18 (5.1)	3 (4.1)

Anti-calcitonin gene-related peptide (anti-CGRP) is a new acute and preventive treatment for migraine. CGRP is a small neuropeptide that activates the trigeminovascular system[17]. Therefore, blocking CGRP signalling has emerged as a new target for migraine treatment[18]. The physiological activity of CGRP is

blocked either by CGRP receptor antagonists or anti-CGRP monoclonal antibodies.

FDA approved anti-CGRP monoclonal antibodies		
Therapy	Dosing, administration route	Indication (in adults)
Eptinezumab (Humanized IgG monoclonal antibodies binds to CGRP)	Quarterly, Intravenous	Prevention of EM & CM
Galcanezumab (Humanized monoclonal antibody binds to CGRP)	Monthly, subcutaneous	Prevention of EM & CM
Erenumab (Human monoclonal antibody binds to CGRP receptor)	Monthly, subcutaneous	Prevention of EM
Fremanezumab (Humanized IgG monoclonal antibodies binds to CGRP)	Monthly or quarterly, subcutaneous	Prevention of EM & CM

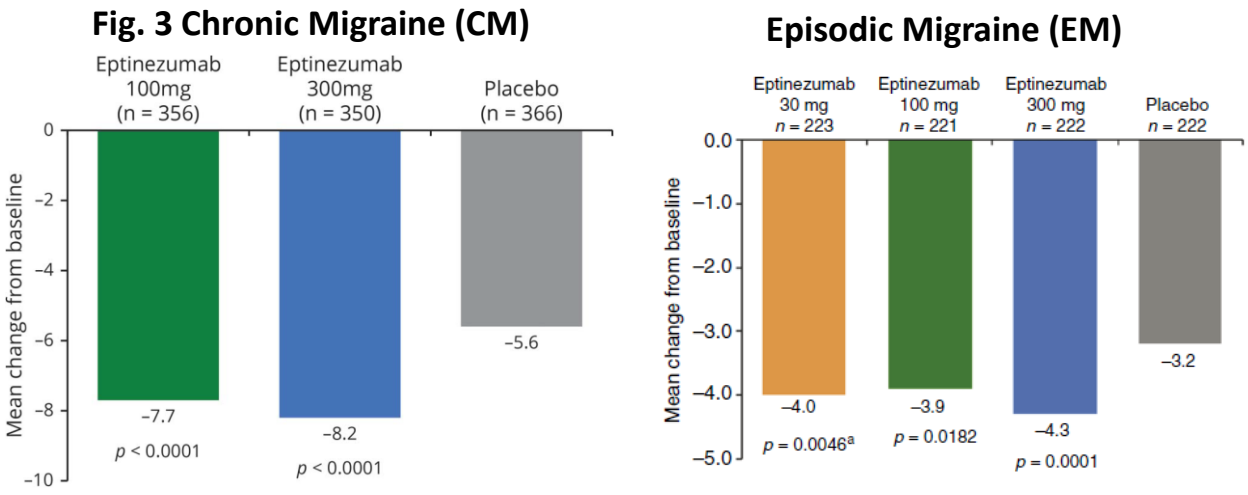
EM: episodic migraine; CM: chronic migraine

Anti-CGRP monoclonal antibodies

Eptinezumab

Eptinezumab received FDA approval on the basis of safety & efficacy results of double-blind, randomized, placebo-controlled clinical trials (PROMISE-1 & 2). A single intravenous injection of eptinezumab reduced monthly migraine days by 50% from the baseline in chronic and episodic migraine patients (Fig. 3)[19,20].

Upper respiratory infections, nasopharyngitis and fatigue were the most common TEAEs reported by ≥ 2% of eptinezumab-treated patients. Further, in CM patients, a single eptinezumab injection reduced the use of acute headache medication (AHM) by 49% from the baseline over 24 weeks. Conversely, patients in the placebo group reported only a 29 % reduction in AHM use[21].

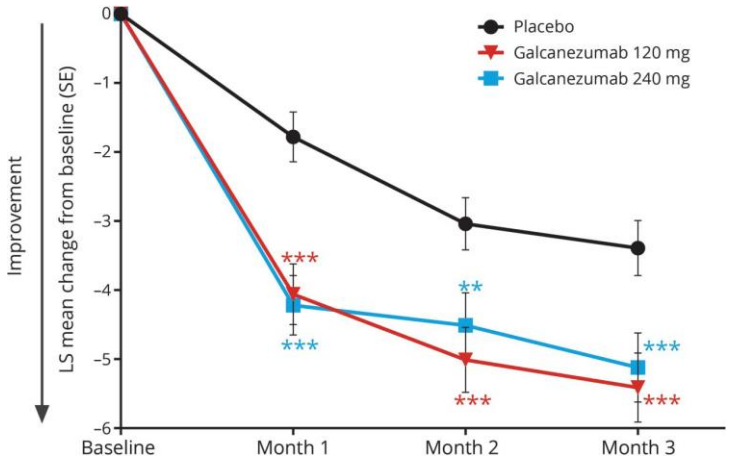


Unlike eptinezumab, which requires administration in the clinical setting, patients can self-administer other anti-CGRP monoclonal antibodies.

Galcanezumab

The safety and efficacy of galcanezumab were evaluated in three clinical trials. In REGAIN study, CM patients took monthly subcutaneous injections of galcanezumab or placebo. Compared to placebo, three months of galcanezumab treatment significantly reduced monthly migraine headache days from the baseline (Fig. 4)[22].

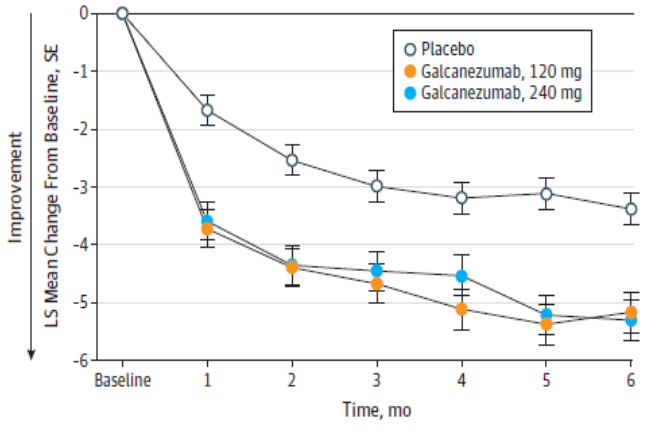
Fig. 4 Reduction in headache days per month



**p < 0.001 vs placebo; **p < 0.01 vs placebo

In EVOLVE 1 & 2 clinical trials, galcanezumab treated episodic migraine (EM) patients reported a significant reduction in the migraine headache days per month relative to baseline than placebo treated patients (Fig. 5)[23,24]. Nasopharyngitis and injection site events (reactions, erythema, and pruritus) were the most reported TEAEs.

Fig. 5 Change from baseline in headache days per month



P < .001.

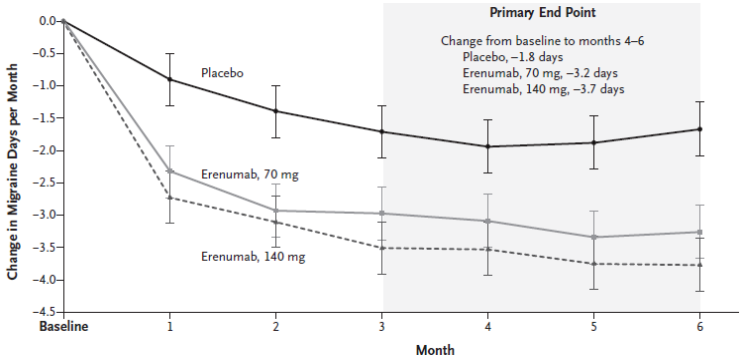
In a recent CONQUER study, galcanezumab showed therapeutic efficacy in patients who were non- responders to other preventive medications (topiramate,

propranolol, amitriptyline, valproate, and Onabotulinumtoxin A). Compared to placebo, galcanezumab treated patients reported ≥ 50% reduction in monthly migraine headache days from the baseline[25].

Erenumab

Goadsby et al. evaluated the efficacy of erenumab in a 6-month long, randomized, double-blind, and placebo-controlled clinical trial. In the final three months of the treatment, erenumab achieved ≥ 50% reduction from the baseline in mean migraine days per month for 43.3% patients in 70 mg group and for 50% patients in 140 mg group. In the placebo group, only 26.6% patients achieved 50% reduction in mean migraine days (Fig.6). The major TEAEs reported were nasophyaryngitis, upper respiratory tract infection, sinusitis, and constipation[26].

Fig. 6 Changes from baseline in migraine days per month



In a two-year-long LIBERTY study, erenumab showed efficacy in treating patients who were non-responders to other preventive medications. 46.7% of patients at weeks 64 of the treatment and 57.2% at weeks 112 reported ≥ 50% reduction from the baseline in monthly migraine headache days. Nasopharyngitis, influenza, and back pain were the most common adverse events associated with the long-term use of erenumab. About 6% of erenumab treated patients reported hypertension[27].

Fremanezumab-vfrm

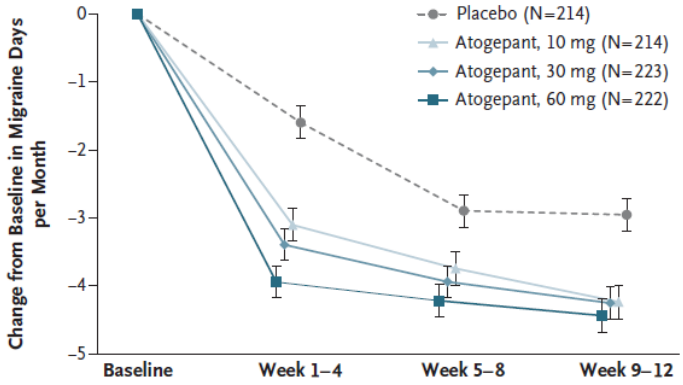
A recent 52-week study showed that both monthly and quarterly doses of fremanezumab effectively reduced migraine days in patients. A quarterly dose of fremanezumab reduced 7.2 migraine days from the baseline, and a monthly dose

reduced eight migraine days in CM patients. In EM patients, the quarterly dose reduced 5.2 migraine days from the baseline and the monthly dose reduced 5.1 days. Injection-site related events (induration, pain, and erythema) were the most reported TEAEs[28].

CGRP receptor antagonists or "gepants" (as they are commonly referred to) have a shorter half-life (~11-12 hours) than anti-CGRP monoclonal antibodies. The shorter half-life of "gepants" provides flexibility in terms of treatment profile and rapid clearance makes "gepants" suitable for people who have to stop the medication in emergency health conditions. "Gepants" are administered orally.

Atogepant is a new "gepant" to receive FDA approval as a preventive treatment. In the phase 3 clinical trial, a daily dose of atogepant (over 12 weeks) significantly reduced the mean number of migraine days from the baseline than a daily dose of placebo (Fig. 7). About 7% of participants in each atogepant group showed constipation as a major adverse event followed by upper respiratory tract infections and nausea[29].

Fig. 7 Changes from baseline in migraine days per month

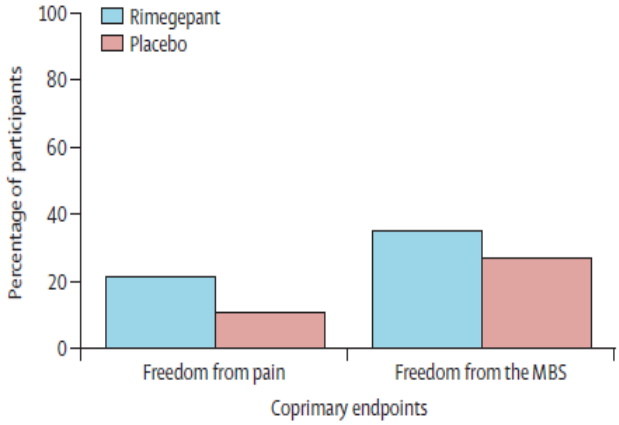


Rimegepant was the first CGRP antagonist to get FDA approval as a preventive medication. It is also approved for the acute treatment of migraine. In a double-blind, randomized, placebo-controlled, phase 2/3 clinical trials, rimegepant showed superiority over placebo in reducing migraine days per month from the baseline (-4.3 days with rimegepant vs -3.5 days with placebo). After three months of

treatment, 49% of patients with rimegepant experienced >50% reduction in moderate to severe migraine days than 41% of patients with placebo. The common TEAEs reported were nasopharyngitis, nausea, urinary tract infection (UTI), and upper respiratory tract infection[30].

The result from another clinical trial indicates the effectiveness of rimegepant in reducing migraine pain and MBS. At 2 h post-medication, 21% of patients were pain-free with rimegepant compared to 11% of patients with placebo. In addition, 35% of patients were MBS free with rimegepant compared to 27% with placebo (Fig. 8). The most common TEAEs reported were nausea, dizziness, and urinary tract infection[31].

Fig. 8 Rimegepant versus placebo for freedom from pain ans freedom from the MBS at 2 h postdose



Ubrogepant was the first CGRP antagonist approved for the acute treatment of migraine. Results from ACHIEVE II phase 3 clinical trial showed the efficacy of ubrogepant in providing freedom from pain and MBS at 2h post-medication (Fig. 9 & 10). About 40% patients could function normally with ubrogepant than 34% of patients with placebo. Nausea was the common TEAEs reported for ubrogepant[32].

Fig. 9 Pain free at 2hr

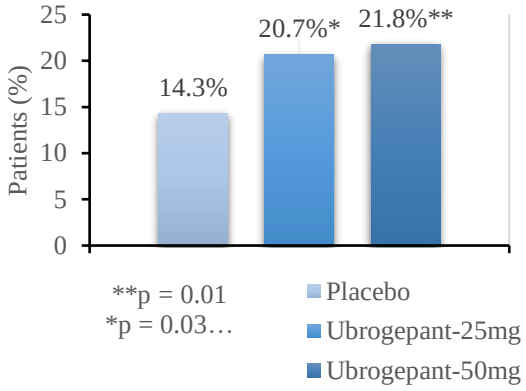
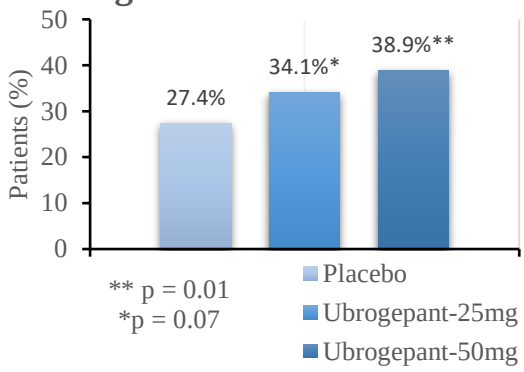


Fig. 10 MBS free at 2hr



Adapted from Lipton RB et al., *JAMA*. 2010;322(19):1887-1898

Conclusion

Migraine is a neurologic condition with a substantial socioeconomic burden. Acute medications (NSAIDs and triptans) and preventive medications (beta-blockers, angiotensin-II receptor blockers, and anti-convulsant) are standard treatment approaches for migraine. However, side effects, poor treatment response, poor adherence, and MOH associated with standard care demand new treatment approaches. The approval of lasmiditan, trudesha, and anti-CGRP therapies provide additional treatment tools to physicians for migraine. To date, these new targets and approaches have shown clinical efficacy in reducing migraine headache days with a better safety profile and suitability for patients at the risk of CVD. However, long-term studies are needed to shed more light on the safety profiles of these treatments.

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