Review

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Novel FDA-approved zavegepant drug for treating migraine

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Abstract

Migraine is a complex neurological disorder characterized by recurring episodes of severe headaches. The pathophysiology of migraine involves abnormalities in neuronal networks, cortical spreading depression, and sensitization of trigeminovascular pathways. The global prevalence of migraine has increased substantially, warranting advancements in treatment strategies. A significant trigger in migraine pathophysiology is calcitonin gene-related peptide (CGRP). Several drugs, such as gepants and monoclonal antibodies (MABs) targeting CGRP or its receptor, have been developed to antagonize CGRP signaling. Zavegepant (Zavzpret), a novel CGRP receptor antagonist, has recently been approved by the FDA for the acute treatment of migraine. Clinical trials have demonstrated its efficacy in providing headache and symptom relief, with a statistically significant percentage of patients achieving freedom from headaches and most bothersome symptoms. Despite mild adverse effects, such as taste disorders and nausea, Zavzpret's overall safety profile remains acceptable.

Keywords: CGRP, gepants, headache, migraine, neurology, neurotransmitter

Migraine is a complex neurological disorder characterized by recurring episodes of moderate-to-severe headache, most often unilateral and generally associated with nausea and increased sensitivity to light and sound[1]. Extensive epidemiological studies identify a variety of risk factors and triggers for migraine episodes. These can be broadly divided into, but not limited to[2,3]:

(1) Biological factors:
   (a) Hormonal imbalances such as estrogen dysregulation;
   (b) Metabolic disorders such as obesity, hyperlipidemia, diabetes, and hypertension;
   (c) Sleep disorders such as insomnia;
   (d) Eating disorders such as anorexia nervosa;
   (e) Neurological disorders such as epilepsy;
   (f) Genetic and epigenetic factors.
(2) Environmental factors such as alcohol and drug abuse;
(3) Demographic factors such as advancing age and female gender;
(4) Psychological factors such as anxiety, stress, phobia, obsessive compulsive disorder (OCD).

HIGHLIGHTS

- Migraine is a complex neurological disorder with severe intermittent headaches.
- A significant trigger in migraine is calcitonin gene-related peptide (CGRP).
- Zavegepant (Zavzpret) is a novel FDA-approved CGRP receptor antagonist.
- Clinical trials have demonstrated its efficacy in providing headache and symptom relief.
- It has mild adverse effects, such as taste disorders and nausea.

Migraine has a complex pathophysiology that involves abnormalities in neuronal networks at different levels of the central and peripheral nervous system. The pathophysiology of migraine is not fully understood, but recent studies have shed light on some of the mechanisms involved. One key hypothesis is that cortical spreading depression (CSD), the phenomenon underlying migraine aura, plays a key role in the pathophysiology of migraine[4]. The trigeminovascular system is also thought to play a role in migraine pathophysiology, with sensitization of peripheral trigeminovascular afferents leading to migraine pain[5]. Other mechanisms that have been implicated include activation of the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway, hypothalamic and dopaminergic abnormalities, gene mutations resulting in neurotransmitter imbalances, overactivation, and central sensitization of pain pathways in the brain. Important neuropeptides involved are serotonin, calcitonin gene-related peptide (CGRP), and pituitary adenylate cyclase-activating polypeptide (PACAP)[6]. Migraine may lead to complications such as status migrainosus, migrainous infarction, migraine aura-triggered seizure, persistent aura without infarction, and work disability[6].

Migraine is one of the most common neurological diseases worldwide, with the global prevalence of migraine being

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estimated to be 1.1 billion [95% uncertainty interval (UI): 0.98–1.3] cases in 2019[7]. In that same year, the national age-standardized point prevalence of migraine ranged from 8277 to 22 400.6 cases per 100 000[7]. Moreover, the global prevalence of migraine has increased substantially over the last three decades. According to the Global Burden of Disease (GBD) 2019 study, the estimated global prevalence of migraine increased from 721.9 million (95% UI: 624.9–833.4) in 1990 to 1.1 billion (95% UI: 0.98–1.3) in 2019[7]. The growing global burden of migraine warrants the need for advancements in its current preventative and curative treatment strategies.

Various medications can be used to treat acute migraines and to prevent their frequency and severity. There is evidence supporting the effectiveness of drugs like acetaminophen, nonsteroidal anti-inflammatory drugs, triptans, antiemetics, ergot alkaloids, and combination analgesics in treating migraines. Acetaminophen and nonsteroidal anti-inflammatory drugs are recommended as the first-line treatments for mild to moderate migraines, while triptans are preferred for moderate-to-severe migraines. However, triptans can be costly despite their effectiveness. Other medications, such as dihydroergotamine and antiemetics, are suggested as second-line or third-line options for certain patients or those with migraines that are difficult to treat. These medications have varying properties, potential side effects, costs, and methods of administration, allowing treatment to be customized based on the pattern and severity of the migraines. Following certain treatment principles, such as taking medication early in an attack and adopting a stratified treatment approach, can help ensure that migraine treatment is cost-effective[8].

The CGRP is the most potent vasodilatory neuropeptide known in migraine pathophysiology. CGRP and its receptor are widely expressed through both the peripheral (PNS) and central nervous system (CNS). In the PNS, it is released from nerve fibers running along meningeal and cerebral blood vessels as well as from the trigeminal ganglion. In the CNS, there are several CGRP-releasing neurons found in the spinal cord, brainstem, thalamus, and cerebellum[9–11]. CGRP's involvement in the aforementioned sites is of particular importance in the pathophysiology of acute migraine attacks[10,11]. Clinical studies provided evidence that, at least in some patients, CGRP was both necessary and sufficient to induce migraine. CGRP levels are elevated in the plasma, saliva, tear fluid, and CSF of patients during spontaneous migraine attacks[12–14]. Not only are CGRP levels elevated during and between migraine, but when CGRP was infused into migraine patients, most developed a delayed migraine-like headache, whereas patients who do not get migraine only got a mild headache[15].

Considering the finding that CGRP is one of the most well-defined triggers of acute migraine attacks, several drugs have been developed to antagonize either CGRP or its receptor. The first molecules to show potential were the CGRP receptor antagonists called 'gepants'. These molecules have a high affinity for the canonical CGRP receptor and prevent CGRP binding and signal transduction. Multiple clinical trials showed that intravenous and oral gepants alleviated migraine symptoms acutely[11]. Some of the notable members of this class of drugs include olcegepant, telcagepant, rimegepant, and ubrogepant[10,11]. Monoclonal antibodies (MABs) targeting CGRP (fremanezumab, galcanezumab, and eptinezumab) and CGRP receptor (erenumab) are another class of drugs able to block CGRP signaling. About half of the patients receiving these antibodies experience a 50% reduction in migraine days[11]. These MABs have the added advantage of being used as a prophylactic for migraine attacks unlike gepants. Overall, current pharmacotherapies for acute migraine have been effective and quite safe so far; however, considering the prevalence of migraine, more drugs are in development. In 2023, FDA filed and approved a new drug to the family of 'gepants', called zavegepant, which, like its family members, is a CGRP receptor antagonist used for the acute treatment of migraine[16] (https://www.neurologylive.com/view/fda-accepts-new-drug-application-intranasal-zavegepant-treat-acute-migraine).

Zavegepant is sold under the brand name Zavzpret by Pfizer Inc. As mentioned previously, it is a CGRP receptor antagonist used for the acute treatment of migraine with or without aura in adults[16] (https://www.pfizermedicalinformation.com/en-us/zavegepant). Zavegepant consists of zavagepant hydrochloride in a buffered aqueous solution containing dextrose, hydrochloric acid, sodium hydroxide, and succinic acid in water. It comes in the form of a nasal spray with the recommended dosage being 10 mg per day, that is, one single spray into one nostril (https://www.pfizermedicalinformation.com/en-us/zavegepant). Nasal administration is of particular benefit to migraine patients since they cannot easily ingest oral medication due to nausea and vomiting[16]. It reaches peak plasma concentrations ~30 min after administration, has a half-life of 6.5 h, and is then mainly removed via the biliary/fecal route (https://www.pfizermedicalinformation.com/en-us/zavegepant). To avoid undesirable drug–drug interactions, Zavzpret should not be co-administered with intranasal decongestants or inhibitors and inducers of organic anion transporting polypeptide 1B3 (OATP1B3) or sodium taurocholate co-transporting polypeptide (NTCP) transporters (https://www.pfizermedicalinformation.com/en-us/zavegepant).

The efficacy of Zavzpret for the acute treatment of migraine with or without aura in adults was demonstrated in two randomized, double-blind, placebo-controlled trials (studies 1 and 2)[17,18]. In both trials, patients with a migraine of moderate-to-severe headache intensity were randomized to receive either Zavzpret or a placebo, after which a percentage of patients achieved freedom from headache and most bothersome symptoms (MBS), which included nausea, phonophobia, and photophobia, was recorded. In study 1[17], the percentage of patients achieving headache pain freedom and MBS freedom 2 h after a single dose was significantly greater in patients who received Zavzpret compared to those who received placebo; Headache Relief: 23.6% Zavzpret vs. 14.9% placebo ($P < 0.001$) and MBS Relief: 39.6% Zavzpret vs. 31.1% placebo ($P = 0.001$). Moreover, 12.4% of patients in the Zavzpret group reported sustained pain freedom for up to 48 h after dose as compared to 8.7% of patients in the placebo group ($P = 0.031$). Study 2[18] also provided similar results; Headache relief: 22.5% Zavzpret vs. 15.5% placebo ($P = 0.011$) and MBS Relief: 41.9% Zavzpret vs. 33.7% placebo ($P = 0.016$). These studies provide substantial evidence for the use of zavegepant as an effective anti-migraine therapy. Additionally, a 12-week randomized controlled trial evaluating efficacy of zavegepant vs. placebo as a prophylactic for migraine is also in progress (https://classic.clinicaltrials.gov/ct2/show/NCT04804033). The trial is primarily investigating the frequency of migraine attacks and is in the process of recruiting participants.

The aforementioned studies[17,18] also evaluated the safety of Zavzpret. In both the trials combined, $N = 1023$ patients were administered Zavzpret while $N = 1056$ were administered placebo. Among the Zavzpret group,18% of patients developed taste disorders such as dysgeusia and ageusia, 4% developed nausea, 3% experienced nasal discomfort, and 2% had vomiting. Less than 1% of patients suffered from a hypersensitivity reaction characterized by facial swelling and urticaria, due to which it is contraindicated in patients with a history of allergy to any components of Zavzpret. If, in any case, major adverse events are observed, Zavzpret therapy should be discontinued and replaced with an appropriate medication.

In conclusion, migraine poses a significant global threat, and the introduction of zavegepant (Zavzpret), a novel CGRP receptor antagonist, marks a significant advancement in its acute treatment. Clinical trials have demonstrated its efficacy in alleviating various symptoms of migraine. While some taste disorders and mild adverse effects have been reported, the overall safety profile of zavegepant is acceptable. However, more clinical studies are required to fully evaluate the potential of Zavzpret and discover its adverse events.

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Author contribution

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