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# Comparison of Eletriptan and Zavegepant therapy in acute migraine: A literature review

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# Abstract

Migraine is a genetically influenced headache characterized by a severe headache, usually affecting only one side and usually accompanied by nausea and sensitivity to light and sound. Migraine attacks can occur repeatedly and are triggered by several factors. Typically, migraine recurs several times a year during childhood and then progresses to several times a week during adulthood. The disease mostly affects people aged 22 to 55 years and can affect about 15% of the population in their productive years. Research regarding the comparison between eletriptan and zavegepant with acute migraine is still rarely known. Therefore, researchers are interested in conducting research on the comparison between eletriptan and zavegepant with acute migraine. This study is expected to be useful for enriching knowledge about the comparison between eletriptan and zavegepant with acute migraine in patients. However, further research is needed to directly compare the effectiveness of these two drugs in a wider and more diverse population.

Keywords: Migraine; Eletriptan; Triptan; Zavegepant; Gepant

#### 1. Introduction

Migraine is a genetically influenced headache characterized by a severe headache, usually affecting only one side and usually accompanied by nausea and sensitivity to light and sound (Ruschel, 2023). Migraine attacks can occur repeatedly and are triggered by several factors. Typically, migraine recurs several times a year during childhood and then progresses to several times a week during adulthood. The disease mostly affects people aged 22 to 55 years and can affect about 15% of the population in their productive years (Burstein, 2015).

Migraine accounts for one-third of the total neurological disease burden and is one of the 15 diseases with the largest increase in disease burden over the past decade. Migraine is one of the 25 leading causes of Years Disabled (YLD). Migraine ranks high on the list of neurological disorders, accounting for more than half of neurogenic YLD, or more than one-fifth of YLD worldwide. This places a heavy burden on migraine sufferers and society. Several clinical and epidemiological studies have validated migraine severity to be an important outcome in evaluating treatment effectiveness in migraine management (Sajobi et al., 2019).

Zavegepant is a third-generation drug of the CGRP antagonist class that works as a CGRP receptor antagonist (Rissardo and Caprara, 2022). This drug is the first in its intranasal route of administration and has good bioavailability compared to previous drugs (Mercer et al., 2020). Eletriptan is a drug from the triptan class that works as a serotonin receptor agonist. Eletriptan also has good affinity among other triptans with serotonin receptors involved in migraine (Mercer et al., 2020).

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Research on the comparative efficacy between eletriptan and zavegepant is still rarely known. Given that eletriptan has better efficacy than other triptan drugs and zavegepant is the latest drug from the gepant group and the first drug with intranasal route administration for migraine. Therefore, researchers are interested in conducting research on the comparative efficacy between eletriptan and zavegepant in acute migraine patients.

# 2. Review Content

# 2.1. Migraine

#### 2.1.1. Definition of Migraine

According to The International Headache Society (IHS), migraine is defined as a chronic neurological disorder that occurs paroxysmally, characterized by moderate to severe headache accompanied by neurological and systemic symptoms, and the potential for recurrence in the future. Typical symptoms of migraine include sensitivity to light (photophobia), sensitivity to sound (phonophobia), and gastrointestinal disturbances such as nausea and vomiting. Migraine is a cyclic disorder with complex symptoms with attacks that can occur at any time and has several phases such as the premonitory phase, aura phase, severe headache attack phase, and finally the postdrome phase (Andreou and Edvinsson, 2019).

# 2.1.2. Epidemiology

Epidemiological studies have shown that migraine has a very high prevalence and has a significant socio-economic and individual impact. According to the 2010 Global Burden of Disease Study, migraine is the third most common medical condition in the world. The highest prevalence is found in Europe, at 15%, while in Africa the prevalence is the lowest, at around 5% (Peck et al., 2016).

In Canada, migraine affects approximately 2.6 million adult women and nearly 1 million men, with a prevalence of approximately 25% in women and 8% in men. As many as 90% of migraine sufferers experience pain of moderate to severe intensity, about 75% experience limitations in activities during an attack, and about 33% require complete bed rest during an attack (Becker *et al.*, 2015).

# 2.1.3. Etiology

Migraine can be caused by a combination of environmental and genetic factors (Piane et al., 2007). Two-thirds of patients with migraine have a family history of migraine (Bartleson and Cutrer, 2010). There may be more than one genetic source acting synergistically with environmental factors at various genomic locations, contributing to disease susceptibility and characteristics in each individual. The genetic basis of migraine is highly complex, and to date, the specific loci and genes involved in its pathogenesis are not fully understood (Ruschel and De Jesus, 2024). Familial hemiplegic migraine, which is one of the migraines from genetic factors, is caused by several gene mutations such as ATP1A2 (ATPase, Na+/K+ transporting alpha two subunit), SCNA1A (sodium voltage-gated channel Type 1 alpha subunit), and CACNA1A (calcium voltage-gated channel alpha 1A subunit) which cause glutamate dysregulation (Anttila et al., 2018).

#### 2.1.4. Classification

According to The International Classification of Headache Disorders 3rd Edition (ICHD-3) guidelines published in 2018, migraines are generally classified into the following types

• Migraine without aura

Migraine without aura, often referred to as generalized migraine, is characterized by headache attacks that last for 4 to 72 hours. The headache is usually felt on one side of the head (unilateral), has pulsating characteristics, moderate to severe pain intensity, and tends to worsen with physical activity. During the attack, other accompanying symptoms include nausea, vomiting, photophobia (sensitivity to light), and phonophobia (sensitivity to sound).

• Migraine with aura

Migraine with aura, also known as classic migraine, is generally not accompanied by motor disturbances. This type of migraine is characterized by visual disturbances in the form of positive symptoms, such as scintillating scotomas resulting from active discharge of central nervous system neurons, as well as negative symptoms, such as loss of visual

function that may be present as visual field defects. In addition to visual symptoms, migraine with aura may be accompanied by sensory symptoms or speech disorders (dysphasia). Headache manifestations are usually accompanied by unilateral visual or sensory symptoms lasting more than 5 minutes but less than 60 minutes.

• Chronic migraine

Chronic migraine is characterized by headaches that occur for 15 or more days a month for more than 3 months. Of these, at least 8 days a month have typical migraine headache characteristics.

• Complicated migraine

This type of migraine includes complications arising from migraine, such as status migrainosus, infarct migraine, or migraine with persistent aura.

• Probable migraine

Probable migraine refers to headache attacks that resemble migraine but does not meet all the diagnostic criteria for a specific type or subtype of migraine. In addition, these attacks also do not meet the criteria for other headache disorders.

• Episodic syndromes that may be associated with migraine

These episodic syndromes often occur recurrently or over a period, especially in children. Although not always migraine headaches, these syndromes are often considered as early manifestations of migraine later in life. Various episodic syndromes associated with migraine include infantile colic, cyclic vomiting syndrome, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis (Gelfand, 2015).

#### 2.1.5. Pathophysiology

The exact cause of headache pain in migraine is still not fully understood. The pathogenesis of migraine involves various components of the central and peripheral nervous system. Today, more modern theories suggest that disruptions in primary neurons may trigger a series of intracranial and extracranial changes that cause migraines. This approach contrasts with the classical vascular theory of migraine which previously held that headache is caused by vasodilation, while aura results from vasoconstriction. Migraine involves activation of the trigeminal system, release of neuropeptides such as CGRP (calcitonin gene-related peptide), serotonin, and neurogenic inflammation (Ruschel and De Jesus, 2024).

Migraine consists of several different phases. The first phase is the prodromal phase, also known as the initial phase or warning signs before the onset of the main headache. This phase is characterized by symptoms such as excessive yawning, increased thirst, drowsiness, specific food cravings, cognitive impairment, and mood swings (Goadsby and Holland, 2019). After the prodromal phase, patients may experience transient neurological symptoms known as migraine aura, usually visual disturbances, which occur shortly before the headache begins. Aura symptoms generally appear within 5 to 20 minutes and rarely last more than 60 minutes (Erdal et al., 2018). Aura can include visual, sensory, speech and motor disturbances, although motor symptoms are rare (Goadsby and Holland, 2019).

The next phase is the headache phase, which is characterized by intense headache pain and is usually localized to one side of the head (unilateral). This pain tends to worsen with physical activity and is often accompanied by hypersensitivity to sensory stimuli, such as light and odors, as well as nausea and vomiting. This phase can last between 4 to 72 hours (Dodick, 2018). After the pain subsides, patients enter the postdromal phase, which is the final stage of a migraine attack. In this phase, patients often experience symptoms such as fatigue, difficulty concentrating, neck stiffness, and decreased cognitive ability (Karsan et al., 2021).

# 2.2. Eletriptan

#### 2.2.1. Mechanism of Action

Eletriptan with the chemical structure 5-[2-(benzenesulfonyl)ethyl]-3-[[(2R)-1-methylpyrrolidin-2-yl]methyl]-1Hindole is a drug from the triptan class used as a first line in the treatment of moderate to severe migraine, or mild to moderate migraine that does not respond to nonspecific analgesics. Drugs in the triptan class work by binding to serotonin receptors (Gilmore, 2011). The mechanism of action of eletriptan includes selective vasoconstriction of extracerebral intracranial blood vessels, inhibition of trigeminal nerve terminals that innervate extracerebral blood vessels, as well as the potential to produce inhibition in the central nervous system at the nucleus caudalis (Humphrey, 2007).

#### 2.2.2. Pharmacodynamics

Eletriptan selectively targets 5-HT(1B/1D) receptors. 5-HT(1B) receptors are located on meningeal and coronary arteries, while 5-HT(1D) receptors are predominantly located on the presynaptic end of the trigeminal nerve. Activation of 5-HT(1B) receptors by agonists triggers vasoconstriction in coronary, cerebral, and peripheral arteries. On the other hand, 5-HT(1D) receptor agonists function to inhibit vascular inflammation in the dura mater while preventing neuropeptide release from the trigeminal nerve endings. This combination of effects, through stimulation of 5-HT(1B/1D) receptors, helps reduce the pain felt during an acute migraine attack (Norteman & Awosika, 2024).

#### 2.2.3. Pharmacokinetics

Once taken orally, the eletriptan is rapidly absorbed through the gastrointestinal tract, with an average time to reach peak plasma concentration (Tmax) of about 1.5 to 2 hours, and maximal concentration usually reached within 2 to 4 hours. The drug has an absolute bioavailability of about 50%, and co-consumption with a high-fat meal can increase the Cmax as well as the area under the curve (AUC) by 20% to 30%. The eletriptan distribution has a volume of about 138 L, with about 85% of the drug bound to plasma proteins. Eletriptan undergoes extensive metabolism in the liver, mainly through the enzyme CYP3A4, which produces several metabolites. Among the metabolites, only N-demethylation is active, with a potency of about 10% of the parent compound. Other metabolites include N-oxides, indole acetic acid derivatives, and glucuronide forms. Elimination of eletriptan and its metabolites occurs through urine and feces, with an average elimination of half-life of about 4 hours in the general population and ranging from 4.4 to 5.7 hours in elderly individuals (Norteman & Awosika, 2024).

#### 2.2.4. Zavegepant

#### Mechanism of Action

Zavegepant, chemically identified as N-[(2R)-3-(7-methyl-1H-indazol-5-yl)-1-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-1-oxopropan-2-yl]-4-(2-oxo-1H-quinolin-3-yl)piperidine-1-carboxamide, belongs to the gepant class of medications used as an abortive therapy for acute migraines. This drug class functions as antagonists of the calcitonin gene-related peptide (CGRP) receptor (Rissardo & Caprara, 2022). Blocking CGRP receptors is believed to reduce neurogenic inflammation and vasodilation, both of which are integral to migraine pathophysiology (Kilinc et al., 2022).

Gepants, along with monoclonal antibodies targeting the CGRP pathway, inhibit the amplification and prolongation of pain processes occurring in the trigeminal ganglion (TG), trigeminal nerve fibers, and dura mater. Specifically, these medications interrupt pain signaling mediated by CGRP through interactions involving glial cells, neurons, and the neurovascular system. Furthermore, gepants may alleviate other bothersome symptoms, such as nausea and autonomic system activation, by acting on the area postrema and sphenopalatine ganglion outside the blood-brain barrier (BBB), regions that receive signals from the trigeminal nerve (Altamura et al., 2022).

#### Pharmacodynamics

Zavegepant is a highly potent, selective, and competitive antagonist of the calcitonin gene-related peptide (CGRP) receptor. Ex vivo studies demonstrate its robust and complete ability to reverse CGRP-induced dilation of human intracranial arteries, a key mechanism implicated in migraine pathophysiology. Importantly, zavegepant does not prolong the corrected QT interval and shows no clinically significant effects on other electrocardiogram (ECG) parameters, ensuring its cardiac safety profile (Dhillon, 2023)

Pharmacodynamically, zavegepant's action is centered on its high affinity for the CGRP receptor, allowing it to effectively inhibit CGRP-mediated signaling. This inhibition not only mitigates vasodilation but also reduces neurogenic inflammation, which is crucial in migraine attacks. Additionally, zavegepant's non-vasoconstrictive mechanism differentiates it from triptans, making it a safer option for patients with cardiovascular risk factors. Its ability to act outside the blood-brain barrier, particularly in the trigeminal system, further enhances its effectiveness in addressing migraine symptoms, including nausea and photophobia. Studies also highlight zavegepant's rapid onset of action, with therapeutic effects observed as early as 15 minutes post-administration (Dhillon, 2023).

#### Pharmacokinetics

Following a single 10 mg intranasal dose of zavegepant, peak plasma concentrations are reached in approximately 30 minutes, with an absolute bioavailability of about 5%. The drug is primarily metabolized by the CYP3A4 enzyme, with a smaller contribution from CYP2D6, as demonstrated in vitro studies. Zavegepant has an effective half-life of approximately 6.55 hours and an average clearance rate of 266 L/hour via the intranasal route. The majority of the drug is eliminated through biliary and fecal excretion, with renal elimination playing a minor role (Dhillon, 2023).

Pharmacokinetically, zavegepant's rapid absorption and short half-life contribute to its suitability as an acute treatment for migraines. Its intranasal administration bypasses the first-pass metabolism, ensuring faster systemic availability compared to oral formulations. The primary route of elimination via the liver and biliary system minimizes the burden on renal clearance, making it suitable for patients with renal impairment. Additionally, the involvement of CYP3A4 and CYP2D6 in its metabolism highlights the potential for drug-drug interactions, which necessitates careful consideration in polypharmacy scenarios. Recent studies have also explored zavegepant's steady-state pharmacokinetics, suggesting that its dosing regimen could be optimized to enhance both efficacy and patient adherence (Dhillon, 2023).

#### 2.3. Efficacy of Both Drugs Against Acute Migraine

Several studies have shown that both eletriptan and zavegepant showed significant clinical efficacy and were well tolerated by patients with acute migraine. The clinical efficacy of both drugs using recommended doses from several clinical trials for the treatment of moderate to severe acute migraine (Capi et al., 2016, Dhillon, 2023).

According to a Japanese study whose subjects were acute migraine sufferers who met the International Headache Society (IHS) diagnostic criteria and classification for migraine. It was found that eletriptan is an effective and safe drug for patients with acute migraine. Doses of 20 mg, 40 mg, and 80 mg of eletriptan were effective in relieving headaches and associated symptoms (Fukuuchi, 2002). An experimental study conducted by Sheftell, et al. (2003) on 1190 patients using eletriptan doses of 20 mg, 40 mg, showed an effective response for patients and showed high consistency of response in multiple attacks, and was well tolerated for the treatment of acute migraine.

In a new drug, zavegepant, whose research was conducted in the United States with subjects with acute migraine who had met the International Headache Society (IHS) criteria for migraine, with the administration of zavegepant nasal spray doses of only 10 mg, it was found that zavegepant was very effective in the treatment of acute migraine, as well as good treatment tolerance and drug safety (Lipton et al., 2023). In a study conducted by Croop et al., (2022) administered zavegepant nasal spray with 3 different doses (5mg, 10 mg, and 20 mg) showed effective treatment for patients with acute migraine, as well as a good safety profile.

# 3. Conclusion

In conclusion, this review explores the comparison of both eletriptan and zavegepant with patients' acute migraine. Eletriptan and zavegepant showed significant clinical efficacy with good safety and tolerability profiles. Eletriptan, a serotonin receptor agonist of the triptan class, has been shown to be effective in relieving headache pain and associated symptoms, and has a high consistency of response. On the other hand, zavegepant, a next-generation CGRP receptor antagonist, offers similar effectiveness via the intranasal route. It also provides a safer alternative for patients with cardiovascular risk compared to triptans as well as for patients who have a history of severe side effects when using triptans.

Both have different mechanisms of action, with eletriptan acting through vasoconstriction of intracranial blood vessels, whereas zavegepant inhibits neurogenic inflammation without vasoconstrictor effects. This difference also allows for personalization of therapy based on clinical needs and patient conditions. However, further studies are needed to directly compare the effectiveness of these two drugs in a wider and more diverse population.

# **Compliance with ethical standards**

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#### Disclosure of conflict of interest

No conflict of interest to be disclosed.

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