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Review Article

"GEPANTS" CGPR ANTAGONIST – A NEW CLINICAL APPROACH TO TREAT MIGRAINE AND NEUROPEPTIDES

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ABSTRACT

The present review is devoted to apparent part of calcitonin gene-related peptide (CGRP) in migraine pathogenesis and to depict the various treatment modalities that are presently available to target this neuropeptide. A veritably incapacitating neurovascular illness, migraines are typified by excruciating headaches that are accompanied by nausea, photophobia, and/or phonophobia, as well as activation of the trigeminovascular system by the production of CGRP Zavegepant through nasal drug delivery system is one of the best approaches which used as a target drug delivery in sustained controlled release fashion. The main advantage to choose the nasal route for drug delivery is to bypass the first hepatic metabolism and direct absorption of drug into the systemic circulation. To provide a relevant background, a brief discussion of CGRP antagonist and Food and Drug Administration approved drugs for migraine treatment will also be considered in this review.

Keywords: Migraine, Calcitonin gene-related peptide antagonist, Gepants, Trigeminovascular system, Food and Drug Administration approved drugs.

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INTRODUCTION

A complex, episodic, and genetic sensory processing condition is "Migraine." Patients who suffer from migraines and sensory hypersensitivity may respond differently to preventative therapies, experience increased cranial autonomic symptoms or difficulty paying attention during everyday activities [1]. They are characterized by a wide range of symptoms, in which headaches serving as the primary symptom. Merely, two out of four headache characteristics — unilateral distribution (one side), pulsatile quality (throbbing), moderate-to-severe pain (more than five out of ten), and exacerbation by physical activity must be present for a migraine. Adults: untreated episodes often 4 h or longer [2]. The case must have endured at least four occurrences with the following migraine characteristics in order to be diagnosed with migraine. The four lapping phases of a migraine occasion might last range from 4 h to 72 h [3].

FOUR OVERLAPPING PHASES OF MIGRAINE

The four overlapping phases of migraine [4-7] are shown in Fig. 1.

Premonitory phase

Non-painful signs can show up days or hours before the headache starts. These symptoms might include increased frequency of micturition, fatigue, thirst, stiff neck, mood swings, trouble concentrating, and yawning [8].

Aura phase

Aura is the name for the temporary localized neurological symptom that occurs before or during some headache episodes in around one-third of migraine sufferers, particularly in women. The most prevalent kind is visual aura (90%) which is followed by sensory aura (30–54%) and linguistic Aura (31%). Since motor, brainstem, and retinal auras are unusual, they occur much less frequently [4].

Headache

The trigeminal sensory pathways that produce pounding pain associated with migraines are activated during this phase. The headache interferes with everyday tasks and gets worse over time or strikes suddenly. Head movement usually makes a headache worse. Usually, it is accompanied by phonophobia, photophobia, nausea, and vomiting [5].

Post drome

During this period, fatigue, sleepiness, trouble concentrating, and intolerance to noise are the most common symptoms. These symptoms will be more severe and persistent the more severe the discomfort. Informally, patients call this phase the "migraine hangover" [6].

ACUTE MIGRAINE MANAGEMENT

Treatments for migraines include both acute and preventative measures. Acute therapy aims to reduce the need for rescue medicine and the likelihood of adverse effects while quickly and effectively relieving headaches and related symptoms and returning functional ability [7]. Optimal acute migraine management degraded chance of episodic migraine to move into chronic migraine. Treatment for acute migraines should focus on eliminating the pain as soon as it occurs, managing attacks no more than twice a week, using the appropriate dosage and formulation, dealing with migraines that cause nausea and vomiting from the start, relieving severe migraines that cause nausea and vomiting, controlling migraines that wake people up from sleep, or treating migraines that progress quickly with parenteral treatments, and considering side effects [9]. There is some drugs mention in Table 1 used for acute migraine treatment.

ROLE OF CALCITONIN GENE-RELATED PEPTIDE (CGRP) IN MIGRAINE

CGRP is an inherently being 37 amino acid neuropeptide with a robust vasodilator effect [21]. Trigeminal sensory neurons innervate these cerebral blood arteries and bear a diverseness of neuropeptides, including as substance P, neurokinin A, and CGRP [22]. It is intriguing to observe that during the migraine headache phase; there is an elevation in plasma levels of CGRP in the external jugular vein, but not of other neuropeptides. As a result, it is now extensively conceded that there is a direct correlation between CGRP and migraine [23].

These neuropeptides may contribute to peripheral and central sensitization of the trigeminal system as well as neurogenic inflammation of intracranial vasculature [24]. The crucial players in the modulation of trigeminal system and other migraine related nervous system structures are neuropeptides. Correlation between neuropeptides and migraine are shown in Fig.2. [25].

"GEPANTS"- CGRP RECEPTOR ANTAGONISTS

Most of the time, CGRP is released by the Dura mater, resulting in neurogenic inflammation and vasodilation [26]. Acute migraine episodes can be treated with a variety of methods, including some innovative drug therapies. Migraine therapy is complicated and requires both preventative measures and immediate care. The most advanced clinical development program for treating migraine attacks is that for CGRP receptor antagonists, or "Gepants" [27]. Ultimately, a more ideal course of therapy and care results from precise evaluation, diagnosis, and cooperation [28,29].

Numerous medications for migraines that target CGRP have been available since 2018 [30]. It includes both injectable monoclonal antibodies (e.g., eptinezumab, erenumab, fremanezumab etc.) [31] and oral small-molecule CGRP receptor antagonists (e.g., ubrogepant, rimegepant, atogepant, and zavegepant) [32-35], mention in Table 2.

Atogepant

It was developed particularly as an oral preventative migraine medication, and a phase II b/III double-blind experiment was conducted to examine its effectiveness [36-38].

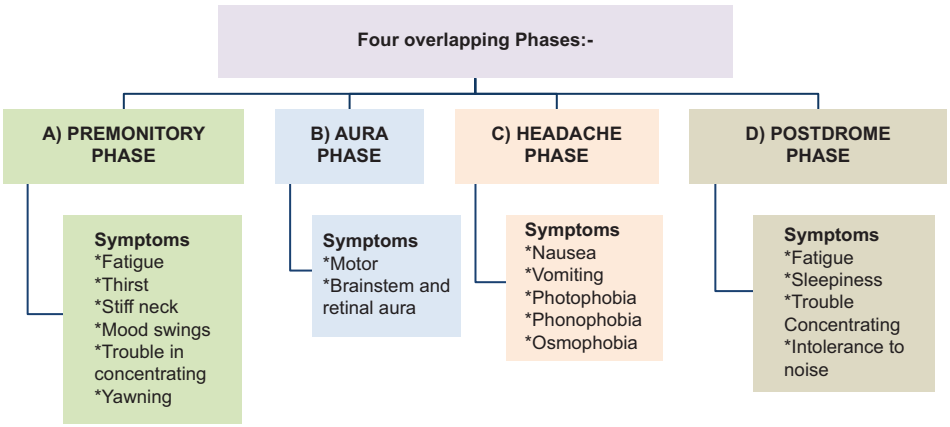

Fig. 1: Phases of migraine

Table 1: Kinds of migraine and medication utilized for migraine treatment

Types of migraine	Type of medication	Active ingredients	Specification	Ref.
Mild to moderate	Orally: Acetaminophen and NSAIDs	Acetaminophen with diclofenac/ibuprofen/ naproxen	An initial dose: Acetaminophen 100 0mg with Diclofenac 50 mg or 100 mg	[7,9]
	Parenteral: NSAIDs	Ketorolac	30 mg (intravenously) 60 mg (intramuscularly)	[10,11]
Moderate to severe	*Triptans*	Sumatriptan Zolmitriptan	Sumatriptan 20 mg (Intranasal) Zolmitriptan 10 mg (Intranasal)	[12,13]
	Dopamine Antagonists	Prochlorperazine, Metoclopramide	Prochlorparazine 10 mg (intravenous) Metoclopramide 10–20 mg (intravenous)	[14]
	Intranasally or Intravenously: Ergots	Dihydroergotamine: A synthetic ergot	1 mg intravenously over 2 min, repeated in 8 h if demanded	[15,16]
	Novel Therapies: Gepants and Ditans	*Gepants*: Ubrogepant, Zavegepant	Ubrogepant: 50 mg or 100 mg orally daily as demanded, an alternate cure can be repeated after 2 h. Zavegepant: intranasally 10 mg formerly 24-h period	[17,18]
		Ditans: Lasmiditan	50 mg, 100 mg or 200 mg daily as per need	[19,20]

NSAIDs: Non-steroidal anti-inflammatory drugs

Table 2: Some FDA approved "Gepants" drugs

Drug name (Company)	Active ingredient	Strength	Dosage form	Route of administration	Approval
Ubrelvy (Abbvie)	Ubrogepant	50 mg and 100 mg	Tablet	Oral	2019
Nurtec Odt (Pfizer)	Rimegepant sulfate	75 mg	Tablet	Orally disintegrating	2020
Qulipta (Abbvie)	Atogepant	10 mg, 30 mg, or 60 mg	Tablet	Oral	2021
Zavzpret (Pfizer)	Zavegepant hydrochloride	10 mg	Spray, Metered	Nasal	2023

FDA: Food and Drug Administration

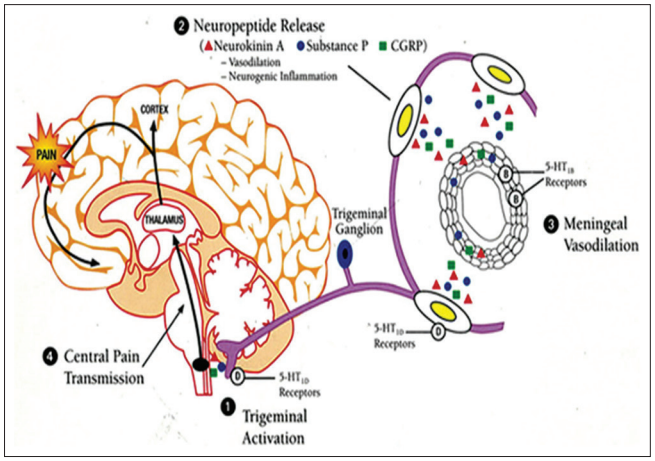

Fig. 2: Correlation between neuropeptides and migraine

Rimegepant

Phase III studies are listed to conclude in early, 2018 and an fresh open-label, long-term safety study (dubbed BHV3000) is currently recruiting and should be finished in early 2019 [39,40]. The USA has licensed Rimegepant, an oral CGRP receptor antagonist, for the immediate treatment of adult migraines. Rimegepant 75 mg dose shown to be both secured and effective in several randomized, placebo-controlled clinical examine [41,42].

Ubrogepant

The first Gepant to be made commercially accessible was ubrogepant. Achieve I and II, two pivotal phase III, multicenter, randomized clinical studies, and were carried out in between 2016 and 2018 [43,44].

Zavegepant

Pfizer is creating Zavegepant, a third-generation small-molecule CGRP receptor antagonist, with funding from Bristol–Myers Squibb to prevent and treat both episodic and chronic migraine [45-47]. Zavegepant nasal spray (ZAVZPRET™) was originally approved in the USA in March 2023 for the instant treatment of adult migraines with or without aura [48-51]. It is a carefully thought-out, regulated drug delivery system that can improve a medication's therapeutic efficacy and get around some of the drawbacks of traditional treatments [52]. To achieve maximal therapeutic efficiency, minimum side effects, and low toxicity, the chemical must be delivered to the target tissue in the ideal quantity within the ideal time frame [53]. There are various approaches in delivering a therapeutic substance to the target spot in a sustained controlled release fashion. One similar approach is using microspheres as carriers for nasal drug delivery system [54-56].

INTRANASAL ROUTE OF ADMINISTRATION

Breathing and odor are the two main purposes of the nasal cavity in humans and other creatures. However, as it filters, heats, and humidifies the air that is inhaled before it reaches the lowest airways, it also provides a significant defensive function. In order to catch inhaled particles and viruses, the nasal cavity is coated with a mucus layer and hairs [57]. The various nasal cavity regions have anatomical and histological traits that enable these activities to be carried out as effectively as possible. According to anatomy, the human nasal cavity occupies the area between the base of the cranium and the roof of the mouth. The ethmoid bones support it over, while the maxillary, inferior conchae, and ethmoid bones support it indirectly [58]. In addition, resonance of produced sounds, muco-ciliary clearance, immunological activities and metabolism of endogenous substances are also integral functions of nasal structures [59,60]. The human nasal cavity has a total volume of 15-20ml and a total surface area of roughly 150 cm^2 [61,62]. It is separated by middle (or nasal) septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the naso pharynx [63]. Both symmetrical halves consist of four areas, shown in Fig. 3:

1. Nasal vestibule
2. Atrium
3. Respiratory zone
4. Olfactory zone.

Characteristics of human nasal epithelium [64-67] are shown in Table 3.

Mechanism of drug absorption through nasal mucosa

Mucus passage is the first step in drug absorption from the nasal cavity [68]. This layer is easily penetrated by tiny, unaltered particles. It could be more challenging for big or charged particles to pass, though. Mucin, the primary protein in mucus, can bind to solutes and stop diffusion. Furthermore, changes in the environment (such as pH and temperature) may cause structural alterations in the mucus layer [69]. These include paracellular transport by cell-to-cell migration, transcytosis by vesicle carriers, and transcellular or simple diffusion across the membrane [70]. Once a medication has passed through the mucus, it can be absorbed via the mucosa in a variety of ways [71]. Limited residence time in the cavity and possible metabolism before entering the systemic circulation are barriers to medication absorption. Although several processes have been suggested, the two that are depicted in Fig. 4 [72] have received the most attention.

Aqueous transport, sometimes referred to as the paracellular pathway, is a component of the first mechanism. This is a passive and sluggish path. This method allowed for the absorption of propranolol, mannitol, and insulin. The molecular weight of water-soluble substances and intranasal absorption has an inverse log-log relationship. Drugs of molecular weights up to 1000 Daltons have a good bioavailability, according to a study of the literature [73]. Permeation enhancers, on the other hand, can raise good bioavailability to at least 6000 Daltons. The second method, which involves transport via a lipoidal channel, also known as the transcellular process, is used to transport lipophilic drugs that show a rate dependency on their lipophilicity. Furthermore, medications can traverse cell membranes via carrier-mediated active transport pathways or tight junctions [74]. For instance, chitosan, a naturally occurring biopolymer derived from shellfish, promotes drug delivery by opening tight junctions between epithelial cells [75].

Barriers to nasal absorption

There are various barriers to nasal absorption [76,77], as shown in Table 4.

Biopharmaceutical consideration

The development of pharmaceutical products is an important process that is directly influenced by its therapeutic goals. The nose is a potentially useful drug delivery organ because of its greater surface area and ease of accessibility. Important biopharmaceutical factors must thus be taken into account before to product development, starting with whether it is meant for [78,79]:

I- Localized delivery
II- Systemic delivery
III- Single or repetitive administration.

The appropriateness of developing a nasal delivery system will depend on its ability to accomplish the therapeutic goals [80]. Numerous clinical, physiological, and anatomical variables need to be taken into account as well [81]. However, integrating the medication into an appropriate vehicle system that offers drug stability and optimal dispensing properties is a significant problem when creating nasal drug delivery formulations. Careful thought must be given to factors including the choice of certain pharmaceutical excipients, delivery systems, and processing techniques [82]. Fig. 5 provides a schematic representation of all the essential elements of an effective nasal formulation.

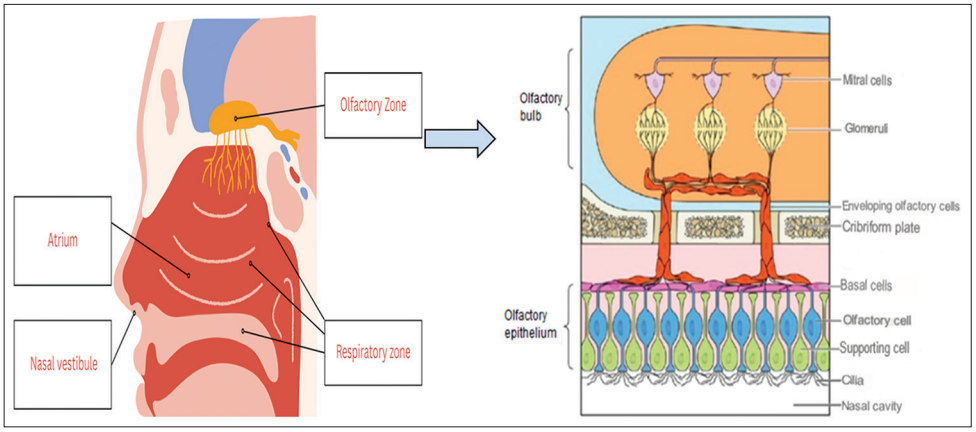

Fig. 3: Anatomy and histology of human nasal cavity

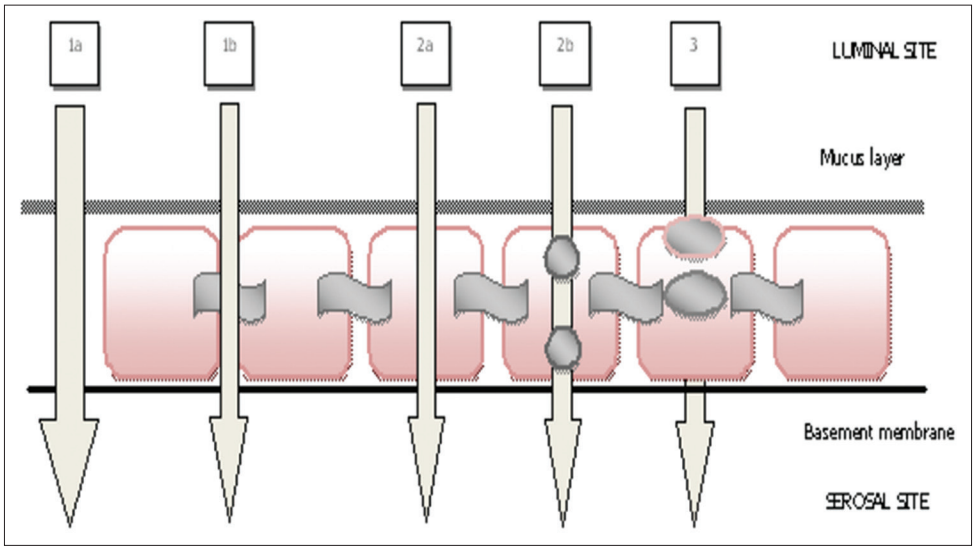

Fig. 4: (1) Paracellular Route (1a) Intercellular Spaces, (1b) Tight Junctions, (2) Transcellular Route (2a) Passive Diffusion, (2b) Active Transport, (3) Transcytosis (modified)

Table 3: Features of human nasal epithelium

Nasal sections	Epithelial cells characteristics	Surface area	Vascularization	Permeability	Functions
Vestibule	• Stratified squamous and keratinized • Epithelial cells with nasal hairs	≈0.6 cm^2	Low	Poor	• Support and protection
Atrium	• Stratified squamous cells • Pseudo stratified cells	Not Found	Low	Reduced	• Support
Respiratory Region	• Columnar non ciliated cells • Columnar ciliated cells • Globet cells • Basal cells	≈130 cm^2	Very high	Good	• Support • Support and muciliary clearance • Mucus secretion • Progenitors of other cell types
Olfactory Region	• Sustentacular cells • Olfactory receptor cells • Basal cells	≈ 15 cm^2	High	Direct access to CNS	• Support • Olfaction perception • Progenitors of other cell types

CNS: Central nervous system

Advantages

1. Rapid and direct absorption into systemic circulation
2. Avoid first-pass hepatic metabolism
3. Less hostile environment than the gastro-intestinal tract, resulting in reduces drug denaturing
4. Improved patient compliance and comfort compared with intravenous administration
5. Rapid absorption, higher bioavailability
6. Avoid irritation in gastro intestinal membrane
7. Reduce chances of over dose
8. Non-invasive
9. Ease of self-medication
10. Infectious disease transmission will be reduced [83,84].

The Food and Drug Administration (FDA) approved nasal preparation other than "gepants" used for migraine treatment

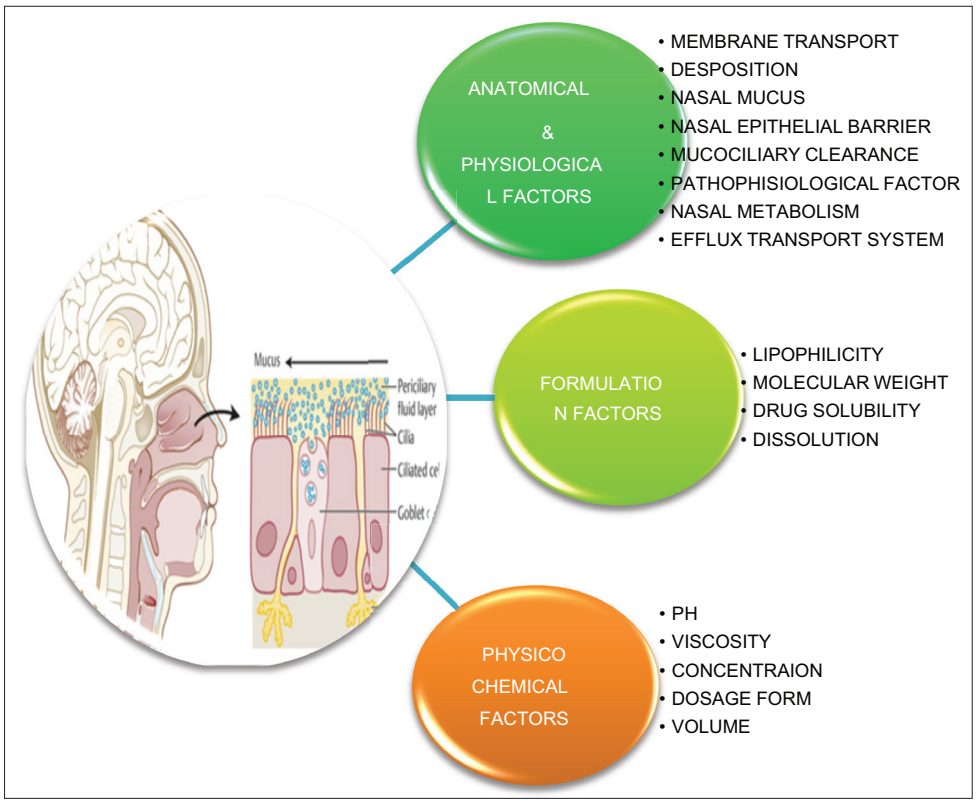

Fig. 5: Parameters consider during nasal product

Table 4: Various barriers to nasal absorption

S. No.	Barriers	Examples
1.	Physiological Barrier	• Nasal mucus • Nasal epithelial barrier • Mucociliary clearance • Pathophisiological factor • Nasal metabolism • Efflux transport system
2.	Physicochemical Barrier	• Drug solubility and dissolution • Molecular weight and size • Compound lipophilicity • pH and pKa
3.	Formulation Factor	• Drug concentration, dose and volume • Osmolarity • Site of disposition

Some examples of FDA approved drugs used for migraine treatment [85,86] are shown in Table 5.

Table 5: Some examples of FDA approved nasal drugs

Drug formulation	Company	Indication	Status
TRUDHESA Dihydroergotamine Mesylate (Spray, Metered; Nasal)	Impel Neuropharma	Acute treatment of migraine	2021
SUMATRIPTAN Sumatriptan Succinate (Nasal Spray)	Padagis Israel Pharmaceuticals Ltd.	Used in migraine	2020
TOSYMRA Sumatriptan (Spray; Nasal)	Upsher Smith Laboratories Llc	Used in the treatment of migraine	2019
ONZETRA XSAIL Sumatriptan (Nasal Powder)	Avanir Pharms Avanir Pharms	Treatment of migraine	2016
ZOMIG Zolmitriptan (Nasal Spray)	Astrazeneca Pharmaceuticals Lp	Treatment of acute migraine	2003
IMITREX Sumatriptan (Nasal Spray)	Glaxosmithkline	Treat migraine headaches and cluster headaches	1997

FDA: Food and Drug Administration

OPPORTUNITIES AND CHALLENGES

To allow the intelligent design of nasal formulations, it is imperative to comprehend the elements that might influence drug deposition, retention, and absorption. There are four monoclonal antibodies (mAbs) have been approved, i.e., erenumab, galcanezumab, fremanezumab, and eptinezumab. Currently only rimegepant, ubrogepant, zavegepant, and atogepant have been approved for migraine prevention [17,87,88]. Before selecting a medication, it is advisable to analyze the patient's specific migraine symptoms to provide tailored therapy that takes into account each patient's unique requirements [89-91]. It's important to note that Zavegepant in nasal formulation seems to be potential new treatment options for people who have trouble swallowing [92-94]. The intranasal spray formulation for migraine management may also enhance general quality of life [95].

CONCLUSION

A very severe neurovascular disorder, migraines may cause nausea, photophobia, phonophobia, and a violent headache. The manufacture of CGRP, which triggers the trigeminovascular system, is their responsibility. The earliest preventative therapies for migraines were two kinds of medications that antagonize CGRP,

i.e., CGRP mAbs and gepants. Novel anti-migraine drugs either directly block CGRP or its receptor or activate the 5-HT1F receptors on trigeminovascular neurons, which prevent CGRP from being produced.

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AUTHOR'S CONTRIBUTIONS

All authors have equally contributed.

CONFLICTS OF INTEREST

No conflicts of interest.

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