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Review Article

Migraines Redefined: A Comprehensive Review of Newly Approved Therapies

T. V. Sowjanya*, Anne Sai Anusha, Vemuluru Kavya Sri, Puli Lahari, Bezawada Sujitha, Shaik Vahin

NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru Dist.

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ABSTRACT

A major cause of quality-of-life problems worldwide is migraine, which is a common neurological condition. Migraine is a complex illness that involves the development of neurovascular and sensory pathways, along with recurrent headaches which often cause nausea, vomiting, photophobia, and phonophobia. This condition is known as migraine. Even though NSAIDs and triptans are effective, some patients experience cardiovascular risks, poor tolerability, and inadequate response. These limitations apply to traditional treatments. New treatments for migraine have radically changed disease management with the introduction of targeted therapies.' Efforts achieved through the use of (gepant, rimegeparent, and ubrogeproient) and monoclonal antibodies (erenumab, derivazolam, eptinezumac) have been found to be more effective, safe, or detectable. In addition, there are newer formulations including intranasal zavegepant, Symbravo combination therapy and Brekiya alternative which also offers more treatment options for both acute and preventive management. Migraines are targeted by these drugs, which reduce the frequency and severity of migraine-related disorders. They have the promise but still face challenges with cost, accessibility and long-term safety data. To optimize outcomes, personalized approaches must incorporate pharmacological advancements with lifestyle modifications and non-pharmacotherapy interventions. The shift towards precision medicine is evident in the development of migraine therapeutics, which offers a renewed sense of hope for improved patient care and quality of life.

INTRODUCTION

Migraine is a common disease affecting people of all ages, characterized by symptoms such as nausea, vomiting, and photo-phonophobia accompanying moderate to severe recurrent headache attack neurovascular origin. It ranks sixth among the most common diseases [1].

***Corresponding Author:** T. V. Sowjanya
Address: *NRI College Of Pharmacy, Pothavarappadu, Agiripalli, Eluru Dist.*
Email ✉: saianusha202094947@gmail.com

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According to data from the World Health Organization, migraine usually begins in adolescence and mostly affects individuals between the ages of 35and45. The period of migraine can vary between 4 and 72h. Although various mechanisms have been suggested for the pathophysiology of migraine, there is no definitive treatment method because the exact cause is not known [2]. Therefore, one of the subjects of drug research and development studies is migraine. Because of the symptoms that occur during a migraine attack, this disease significantly reduces the patient's quality of life[3]. Even if only one of these symptoms occurs, the need to access available medications during a migraine attack increase. Suicidal ideation may occur in patients with migraine attacks due to the intense pain they feel.

Premonitory Phase: Early signs of distress, such as tiredness, mood swings, food craving or irritable state [4].

Aura Phase: The aura phase is the period of sensational disturbances, sensory changes, or speech difficulties that occur before the onset of headache [5].

Headache Phase: Moderate up and down blemishes with nausea, vomiting along with photophobia and phonophobia [6].

Postdrome phase: Once the headache is under control, patients may feel tired, weak, or struggle to concentrate [7].

Fig. No 1: Migraine Head-Ache

Drugs For Migraine Relief

1. Rimegepant
2. Atogepant
3. Zavegepant
4. Symbravo
5. Brekiyas
6. Ubragepant
7. Eptinezumab
8. Fremanzumab
9. Erenumab
10. Rizatriptan

1. Rimegepant

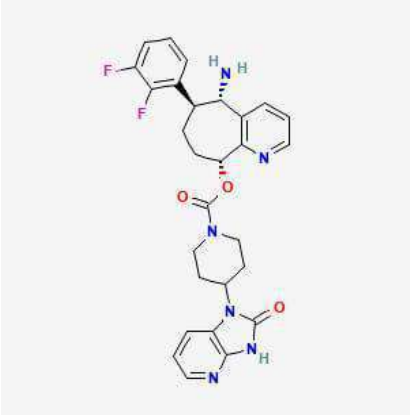

Fig. No 2: Structure of Rimegepant

The nucleus of the nexus contains a fused heterocyclic system, with imidazole and pyridine as its active members. Rimegepant's unique mechanism of action (MOA) distinguishes it from older migraine drugs like triptans, making it a significant advancement in medicinal chemistry for migraine treatment. Unlike other drugs, Rimegepant prevents the pronociceptive and vasodilatory effects of CGRP, which is elevated during migraine attacks [8]. While this MOA directly targets a critical pathway in the onset of migraines, it does not result in vaginal constriction, making patients with pre-existing cardiovascular conditions who are contraindicated to use triptans safer. Among other things, in the realm of medicinal chemistry, Rimegepant stands

out as an orally bioavailable small molecule, which was previously difficult to achieve for CGRP receptor antagonists. Its imidazopyridine derivative, which has a chemical structure that allows for effective oral absorption and pharmacology, contributes to its therapeutic value. Its primary metabolism is regulated by CYP3A4 and to a lesser extent by the cAMP2C9, which means that potential drug-drug interactions should be carefully monitored by highly potent enzymes that inhibitor induce the seen enzyme functions. The safety profile and efficacy of this product have been consistently demonstrated by clinical trials, with only mild side effects like nausea and dizziness occurring frequently, and no significant liver or cardiovascular toxicity found.

2. Atogepant:

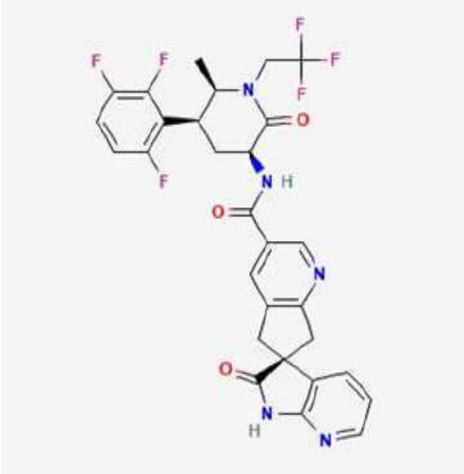

Fig. No 3: Structure of Atogepant

The molecule has a core structure made up of a pyridine ring system, which is a six-membered ring containing three nitrogen atoms. This ring is connected to a piperidone group, which includes a ketone, and also has carbamate and urea groups attached. Atogepant, also known as Qulipta, is a modern drug used in medicine. It is a small molecule that blocks the calcitonin gene-related peptide receptor [9]. It can be taken by mouth and is easily absorbed into the body. The molecule has a complex structure with specific stereochemistry and fluorine atoms that help it bind well to its target and stay active in the body for a long time. This helps prevent the chain of events that lead to migraine pain and related issues like inflammation and sensitivity in the nervous system.

3. Zavegepant:

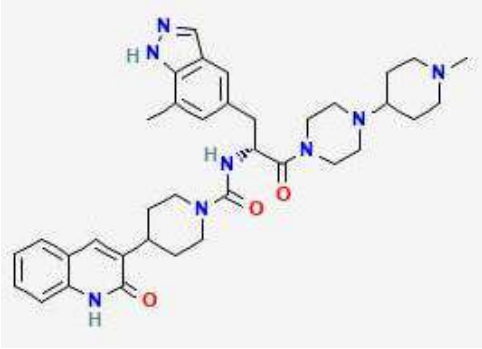

Fig No. 4: Structure of Zavegepant

The fusion bicyclic system in NUCLEUS comprises of the Imidazole ring (5 nitrogen atoms, 2 members), Pyridine RING (6 members, 1 nitrogen element, and two rings). It is known as "Imidozole-1.2-a"pyridine. What is the chemical structure of this compound The heterocyclic components include the piperidine ring, Triazole-like fragments (in analogues during lead optimization), urae, and amide linkages. Zavegepant's nucleus is responsible for blocking the CGRP receptor [10]. Another important neuropeptide involved in migraine pathology is CGRP. Sensory nerves in the trigeminal system release CGRP during migraine attacks, leading to vasodilation and increased neuronal excitability. the usual way to use Zavegepant is by spraying it into one nostril and letting it in. Rapid absorption through the nasal route results in a relatively quick start of action, with some patients experiencing pain relief within 15 minutes and discomfort by two hours. It is not meant to be used as if it were preventive; rather we recommend it during an active migraine episode.

4. Symbravo

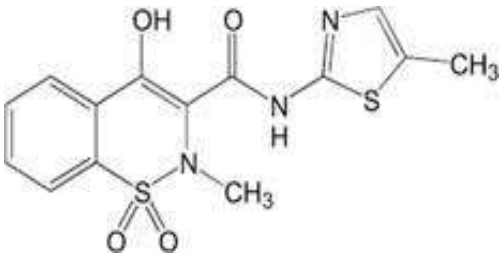

Fig. No. 5: Structure of Symbravo

The oxicam class includes the meloxic scaffold, which is composed of a 1,2-benzothiazine-3-carboxamide. A heterocycle of benzothiazine with enolic and carboxamide functionalities is the foundation. The FDA has approved Symbravo, a new combination drug for adults with or without auras, as 'the most acute form of treatment for migraine headaches'. The goal is not to prevent migraines or treat other types of headaches, such as cluster headaches [11]. The "nucleus" in "Symbravo nucleus" is probably a reference to the drug's central mechanistic approach or its primary therapeutic function. In the realm of medicinal chemistry, Symbravo offers an innovative approach that merges two well-established drug classes: one triptan and an NSAID, specifically rizatriptans and meloxicam. The selective serotonin 5-HT$_1B/1D$ receptor agonist Rizatriptan. It is believed that migraine treatment involves vasoconstriction of cranial blood vessels, inhibition of neuropeptide release from trigeminal nerve endings, and inhibition pain signal transmission. The selective inhibitor of COX-2 in meloxicam, an NSAID, is intended to be effective. By inhibiting the production of prostaglandins, which are essential mediators in migraine pathophysiology, it reduces inflammation and pain. Symbravo's unique feature in medicinal chemistry is its formulation. The technology used in it is a proprietary type called MoSEICTM, which was developed by Axsome Therapeutics. This technology is intended to increase the solubility and absorption of meloxicam, which will speed up the onset of action. Symbravo's approach involves delivering both rizatriptan and meloxicam in rapid delivery, with the aim of early intervention in various aspects of the migraine cascade. This includes targeting neurogenic inflammation (via Valtrex am) and potentially affecting vasodilation and pain transmission (by CGRP). The multi-mechanistic approach to migraine addresses its complex and heterogeneous nature, highlighting the involvement of various physiological pathways. The "nucleus" treatment by Symbravo targets multiple key pathways in migraine pathophysiology to deliver immediate and long-lasting relief, combining the active ingredients of triptan with NSAIDs.

5. Brekiya

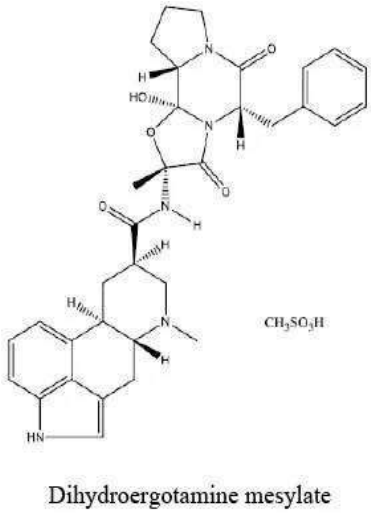

Fig No. 6: Structure of Brekiya

Ergoline nucleus serves as the foundation for an ergot alkaloid core that functions as its core heterocycle. Tryptophan and lysergic acid are used to create the tetracyclic system.? A cyclopentane and piperidine ring system is fused to the indole moiety. High affinity at serotonin (5HT) and other biogenic amine receptors is the primary contributor to the multi-ring scaffold's pharmacological activity. An ergot alkaloid derivative called Dihydroergotamine (DHE) is the

main ingredient in Brekiya, which is commonly used to treat adults with migraines with or without aura and acute cluster headaches. The therapeutic effects of DHE can be explained by its intricate interaction with different neurotransmitter receptors, including serotonin (5-HT) receptor. Initially, its MOA acts as an antagonist at the 5-HT$1B$ and 5-THUNDER-HOT $/D ($). Vasoconstriction is believed to be alleviated by the activation of receptors on cranial blood vessels that trigger vasodilation in migraine. In addition, DHE's impact on presynaptic nerve terminal 5-HT$_1D$ receptors can hinder the release of pro-inflammatory neuropeptides, which could potentially alleviate pain. Hence, DHE's broad receptor binding profile, in addition to its alpha-adrenergic receptors, sets it apart from other acute migraine treatments and contributes to the vasoconstrictive properties. The strong influence of the multi-receptor interaction is crucial in halting the migraine cascade [12]. DHE is a valuable treatment for migraine patients who experience severe nausea and vomiting due to their attacks, or those who respond poorly to oral triptans due in some cases to issues like gastroparesis during an attack. The administration through the skin instead of the gastrointestinal tract results in more consistent and rapid absorption. This is achieved by bypassing the gut. In spite of this, just like all ergots, DHE can cause serious vasoconstrictive complications, particularly when taken together with potent CYP3A4 inhibitors that can elevate DHA plasma levels. This requires careful patient selection and monitoring in clinical practice. convenience, the company hopes to make a well-established compound more easily accessible for acute headache relief.

6. Ubrogepant

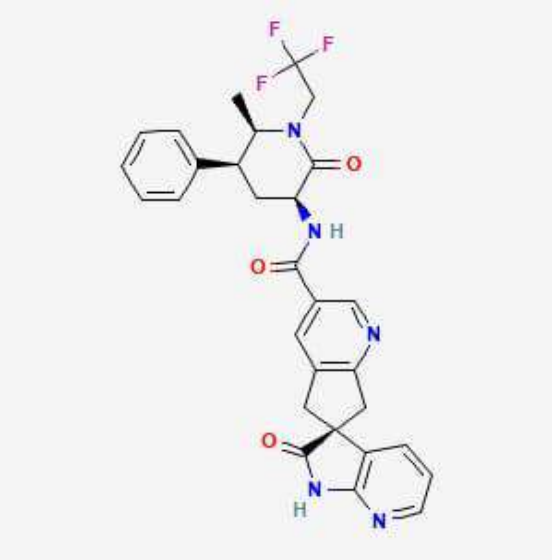

Fig No. 7: Structure of Ubrogepant

NUCLEUS: Imidazole[4,5-b] pyridine. A fused heterocyclic ring system composed of: Imidazole (5-membered ring with two nitrogen atoms), Pyridine (6-membered ring with one nitrogen atom) Ubrogepant is a groundbreaking oral small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist approved for the acute treatment of migraine with or without aura in adults. Its medicinal chemistry centres on its highly specific and selective binding to the CGRP receptor, distinguishing it from earlier migraine treatments. Migraine pathophysiology involves the release of CGRP, a neuropeptide that plays a

crucial role in vasodilation of cerebral blood vessels and transmission of pain signals in the trigeminal system. By competitively binding to and blocking the CGRP receptor, Ubrogepant prevents CGRP from exerting its effects, thereby attenuating neurogenic inflammation and pain signal transmission associated with a migraine attack [13]. This mechanism of action avoids the vasoconstrictive properties of triptans, offering a safer alternative for patients with cardiovascular risks.

7. Eptinezumab

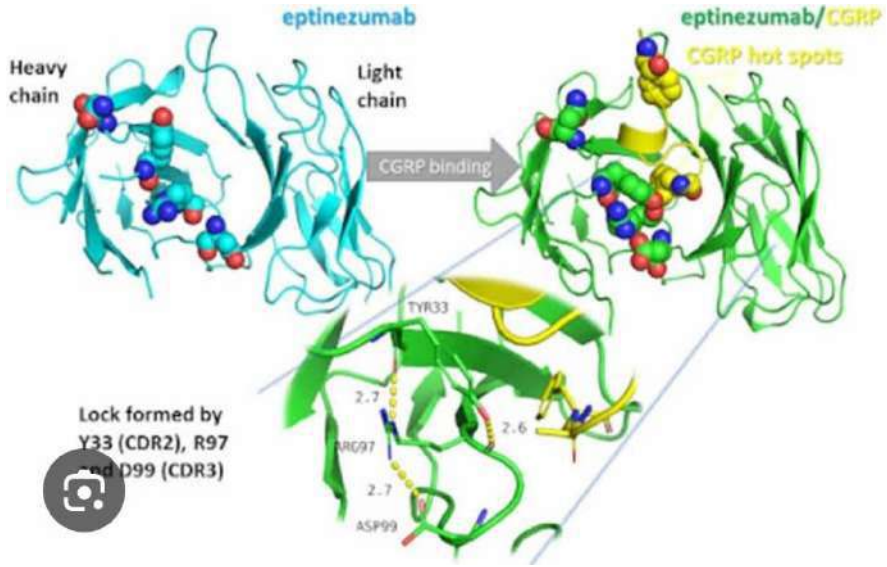

Fig No. 8: Structure of Eptiezumab

A monoclonal antibody (mAb) called Eptinezumab, specifically a humanized IgG1, is used to treat NUCLEUS. Synthetic drugs like imidazole or indole have a traditional small-molecule chemical nucleus that is absent in biologic drugs. This makes them unique. Instead, it is a complex structure of antibodies made from proteins that contain variable heavy and light chains, which enable specific binding to CGRP through compounds called complementary-determining regions (CDRs). Targeting the CGRP peptide in the bloodstream is possible for Eptiezumab's IgG1 antibody backbone, which functions as an "nucleus" Eptinezumab can activate MOA by highly affinity-binding its respective alpha and ßbeta forms to the common carrier chain reaction (CGRP) ligand. The direct binding of eptinezumab to CGRP receptors prevents them from interacting with vascular smooth muscle cells and neurons, which in turn inhibits the vasodilatory and pro-inflammatory effects associated with its release [14]. In contrast to other monoclonal antibodies that target CGRP, eptinezumab works by keeping the ligand at the receptor. This keeps it from reaching the binding site. CGRP is rapidly reduced to activate the visuomotor activity associated with migraine. Ipţizumab is a preventive medication that is indicated for adults with migraines, both frequent and chronic. It is given through IV injection for about 30 minutes, usually every 12 weeks. The quarterly dosing schedule provides patients with a convenient and predictable treatment option. Clinical trials, including the PROMISE-1 and PROMOTION-2 studies, have demonstrated that eptinezumab significantly reduces monthly migraine days (MMDs) more quickly than placebo, with benefits observed as early as day 1 post-infusion. Common side effects include nasopharyngitis and hypersensitivity reactions.

8. Fermanezumab

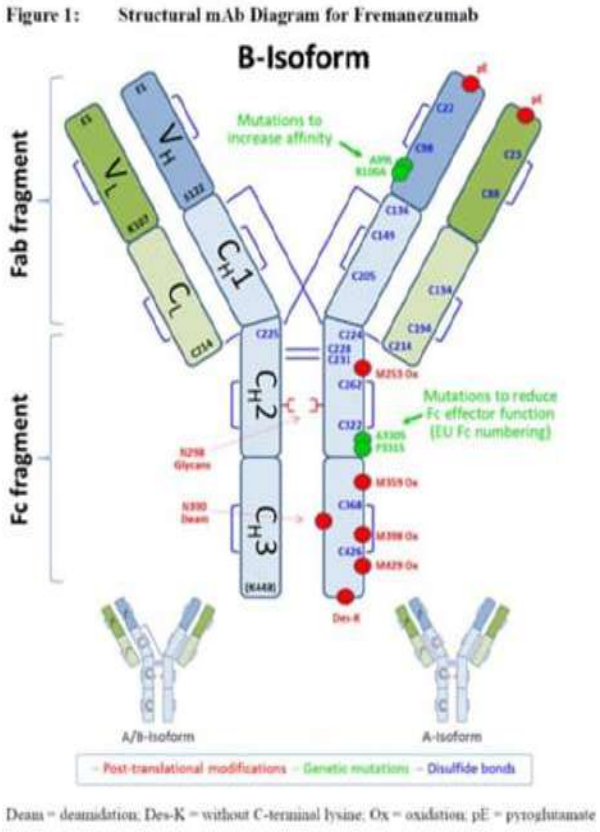

Fig No. 9: Structure of Fermanezumab

The small-molecule nucleus that is present in synthetic drugs is absent in Fremanezumab. The recombinant human IgG2 monoclonal antibody is made up of Varying regions are formed in chains with heavy and light weights to facilitate binding to CGRP ligand. Antibodies are typically Y-shaped with Fc (constant) and Fab (variable) regions. An important medicinal chemistry factor in migraine prevention is the humanized monoclonal antibody (IgG2a) that is Fremanezumab. Alpha and oeuvres isoforms of the calcitonin gene-related (CGRP) ligand are highly selectively bound by MoA [15]. The selective targeting of CGRP by sequestering it prevents binding to its receptor and thus interrupts the important pain signalling and neurogenic inflammation pathways involved in pathophysiology, making this approach a significant advancement over non-specific migraine therapies. In the field of medicinal chemistry, fremanezumab is distinguished by its large protein structure (about...). 148. The elimination half-life of this drug is extended to around 31-39 days, making it possible to receive subcutaneous treatment on a monthly or quarterly basis with three 225 mg injections. The key advantage of fremanezumab is its metabolism, which differs from that of small molecules, as it is broken down into smaller peptides and amino acids through catabolic processes to minimize drug interaction potential.

9. Erenumab

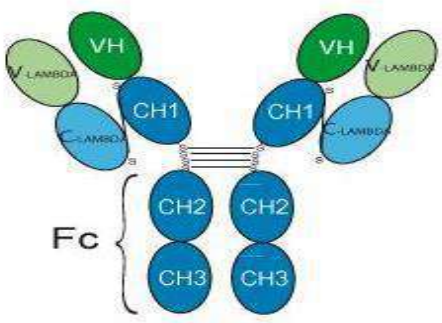

Fig No. 10: Structure of Erenumab

A small-molecule nucleus, such as aromatic rings or heterocycles, is not present in Erenumab. Contains: Heavy chain and light chain variable regions engineered to specifically bind to the CGRP receptor. ". It is a monoclonal antibody for human IgG2 that functions structurally. In the field of medicinal chemistry, Erenumab is an innovative new therapeutic agent that targets migraine prevention and is a human monoclonal antibody (IgG2 class). Erenumab selectively and directly targets the CGRP receptor, which is essential for migraine pathophysiology due to its role in pain signalling and vasodilation. [16]. Erenumab selectively blocks the CGRP receptor by binding with it at high levels, which inhibits downstream signalling pathways that cause migraine pain and associated symptoms. This prevents the reduced cAMP production required by other signals from ligands. Both episodic and chronic migraines in adults can be prophyll owed by erenumab, which is administered through subcutaneous injection once a month. Despite not being a cure for acute migraines or providing instant relief, it has been proven effective in clinical studies by significantly reducing the incidence of migraine headaches and the need for medication specific to acute cases. Its creation represents a significant leap forward in the management of migraines, providing individualized care for patients who may have previously received or tolerated conventional oral preventive therapy.

10. Rizatriptan

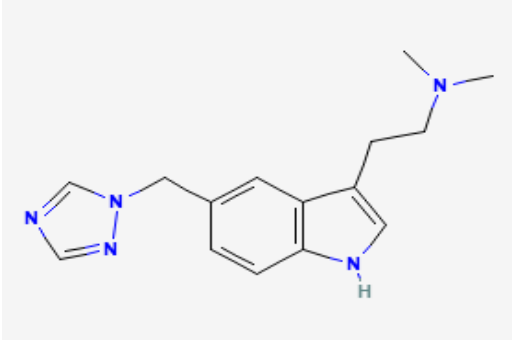

Fig No.11: Structure of Rizatriptan

The Indole nucleus is located within Rizatriptan. The mechanism of action is characterized by selective agonism at the receptors on serotonin 5-HT$1B$ and 5-TH-1D $. Pro-inflammatory neuropeptides are released and intracranial blood vessels are dilated during a migraine attack [17]. By interacting with these receptors, Rizatriptan produces results. Visconti ostomy reduces the throbbing pain caused by migraines, as it narrows blood vessels in the intracranial extracerebral region. The primary pathway for this action is thought to be the 5-HT$_1B$ receptors. Blocking the release of neuropeptides, such as CRP, which are released by Rizatriptan, and contribute to the inflammatory response. The transmission of pain signals is inhibited by activating 5-HT$_1D$ receptors on peripheral trigeminal sensory nerve terminals in the meninges and central terminal peaks in brain stem sensory nuclei. Rizatriptan is an effective treatment that provides relief within

30 minutes to 2 hours. It can be taken by mouth or through oral means, including tablets and disintegrating tablets. Paediatric patients aged 6-17 use Rizatriptan, with the dose varying by body weight. It is frequently combined with over-the-counter painkillers and anti-sickness medications for optimal relief. [Note]. Nonetheless, rizatriptan should only be administered after a clear diagnosis of migraine and is not advised for use in those with hemiplegic or basilar migraines, which have heightened risk of stroke.

CONCLUSION

Recent advancements in migraine therapeutics have revolutionized the treatment landscape, moving beyond conventional therapies like triptants and NSAIDs. The approval of novel drug classes such as CGRP monoclonal antibodies (erunumab, fermanezumab, eptinezumab, brekiya) and oral CGRP receptor antagonist (gepants like Rimegepant, Ubrogepant, and atogepant) has provided targeted, mechanism-based options with improved efficacy and tolerability. In addition, the introduction of Lasmiditan (a selective 5HT1F agonist) offers a non-vasoconstrictive alternative for patients with cardiovascular risk factors. These innovative therapies not only reduce the frequency and severity of migraine attacks but also enhance patients' quality of life by minimizing side effects and improving adherence. However, the high cost and limited accessibility remain challenges. Future research should focus on long-term safety data, personalized treatment strategies', and combination therapies to optimize outcomes. Overall, the newly approved drugs signify a paradigm shift toward precision medicine in migraine management.

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