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NOVEL APPROACHES IN TREATMENT OF MIGRAINE: NEW ANTI-MIGRAINE DRUGS

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ABSTRACT: -

Migraine is a long-lasting neurovascular condition that impacts more than one billion people around the globe, making it the sixth most common illness worldwide. It is marked by recurring, moderate to severe pulsating headaches, frequently accompanied by symptoms such as nausea, vomiting, and increased sensitivity to light and sound (photo-phonophobia). Although migraines usually start in adulthood, they are more prevalent in women, with rates approximately double those seen in men.

In the acute management of migraine, analgesics are commonly used to provide rapid pain relief. For chronic migraine sufferers, a range of treatment options is available. Over the past few years, significant advancements in migraine management and prevention have been made, particularly with the introduction of novel drugs. Medications such as lasmiditan, ubrogepant, rimegepant, and monoclonal antibodies—including erenumab, fremanezumab, galcanezumab, and eptinezumab—have been introduced to the U.S. market, with several also being accessible in Europe. This article examines the safety profiles of new antimigraine treatments on a global scale, emphasizing the potential for drug-drug interactions (DDIs) and drug-food interactions (DFIs). It specifically highlights the interactions between gepants and lasmiditan with serotonergic medications, CYP3A4 inhibitors and inducers, along with inhibitors of breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp). For monoclonal antibodies, an article explores the pharmacodynamic interactions related to immune system modulation, emphasizing how these drugs may influence immune responses.

As migraine therapies advance, it is essential to comprehend the safety profiles of emerging medications and their possible interactions to enhance patient care and reduce adverse effects.

KEYWORDS: - Migraine, Migraine Headaches, neurovascular disorder, Anti-Migraine drugs, CGRP (calcitonin gene-related peptide), Anti-CGRP Monoclonal Antibodies, Trigemino-vascular Therapies, Cannabis-Based Therapies.

INTRODUCTION: -

Migraine is a neurological condition that may present as either acute or chronic, marked by recurring, usually one-sided, throbbing headaches. These episodes typically endure for a duration of 4 to 72 hours and can differ in severity. Individuals suffering from migraines frequently experience various hypersensitivities, such as photophobia (sensitivity to light), phonophobia (sensitivity to sound), osmophobia (sensitivity to odors), along with symptoms like nausea and vomiting.

In Europe and North America, approximately 11–12% of the population experiences migraines, with women comprising around 75% of those affected. Chronic migraine occurs when frequent episodic migraines transition into more persistent attacks, increasing both their frequency and duration. Over time, the nature of some attacks may shift, resembling the pain profile of tension-type headaches rather than traditional migraines. Chronic migraine sufferers may also develop medication-overuse headaches, which can be challenging to differentiate from normal headache patterns.

The pathophysiology of migraine encompasses intricate interactions among the cortical, subcortical, and brainstem areas of the brain. Migraines frequently result in a range of autonomic, cognitive, and emotional symptoms, impacting not only the head but also the body's physiological processes.

Several factors are known to trigger migraine attacks. These include environmental stimuli such as light, noise, and odours, as well as lifestyle factors like sleep disturbances (too little or too much sleep), irregular meal patterns, stress, physical exertion, and hormonal fluctuations. These triggers may cause disruptions in the normal physiological processes, leading to heightened sensitivity to external stimuli.

Phonophobia, or an increased sensitivity to sound, is a common symptom of migraines. This condition can make everyday environments feel overwhelming to migraine sufferers, prompting a desire to avoid noisy places or activities.

In sum, migraine is a multifaceted disorder that extends beyond just a headache, affecting a wide range of physical and sensory systems. Understanding the complexities of migraine triggers and symptoms is crucial for effective management and treatment.

Fig no. 1 Factors Stimulating Migraine

PATHOPHYSIOLOGY OF MIGRAINE: -

Migraine is a condition characterized by a complex and multifaceted pathophysiology that engages both the central and peripheral nervous systems. The physiological process of a migraine attack can be categorized into several distinct phases, each exhibiting unique mechanisms: the prodrome, the acute aura and/or headache, and the postdrome.

The core of an acute migraine episode lies in the activation of the trigeminal vascular system, which encompasses essential components such as the trigeminal nuclei located in the brainstem (notably the nucleus caudalis), the trigeminal ganglia, and the ophthalmic branch of the trigeminal nerve (V1). This branch is vital for innervating blood vessels and is tasked with relaying pain signals from the meninges. The activation of this pathway triggers the release of neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), all of which are associated with the pain mechanisms involved in migraines. Elevated levels of CGRP and PACAP-38 are noted during migraine episodes, and both peptides have been demonstrated to provoke headache symptoms similar to those of migraines when administered.

Despite thorough investigation, a conclusive pathological condition or physiological disorder that universally triggers migraines has yet to be established. Initial theories concerning the vascular basis of migraines emerged in the 20th century. In 1938, Harold Wolf proposed that migraines might result from vascular irregularities, specifically the dilation of blood vessels. This theory posits that the expansion of extracerebral blood vessels, which are constricted during a migraine, plays a role in alleviating pain. The process of vasodilation leads to inflammation of adjacent nerves, which subsequently irritates nociceptive fibers, resulting in the headache. This vascular hypothesis gained further traction with the development of ergotamine-based treatments in the 1940s, following the discovery that migraine attacks were associated with changes in vascular tone, particularly vasodilation. Ergotamine was used as a vasoconstrictor to alleviate migraine symptoms.

In addition to its role in vasoconstriction, serotonin has been recognized for its involvement in the pathophysiology of migraines, primarily due to its vasoconstrictive properties. Early treatment approaches incorporated serotonin supplementation to counteract the effects of vascular dilation. Over the years, various pharmacological options have been investigated for migraine prevention, including β-blockers, angiotensin receptor blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and calcium-channel blockers.

Preventive strategies have also included alternative therapies such as magnesium supplementation, botulinum toxin injections, and a range of herbal remedies. Recent studies indicate that the trigeminovascular system, which encompasses sensory trigeminal nerve fibers, cerebral blood vessels, and the dura mater, is crucial in the development of migraine headaches. During a migraine episode, the activation of trigeminovascular neurons leads to the release of vasoactive peptides that trigger inflammation and pain. This system represents both an anatomical and physiological target for migraine treatment, aiming to modulate the associated neural and vascular mechanisms to relieve symptoms.

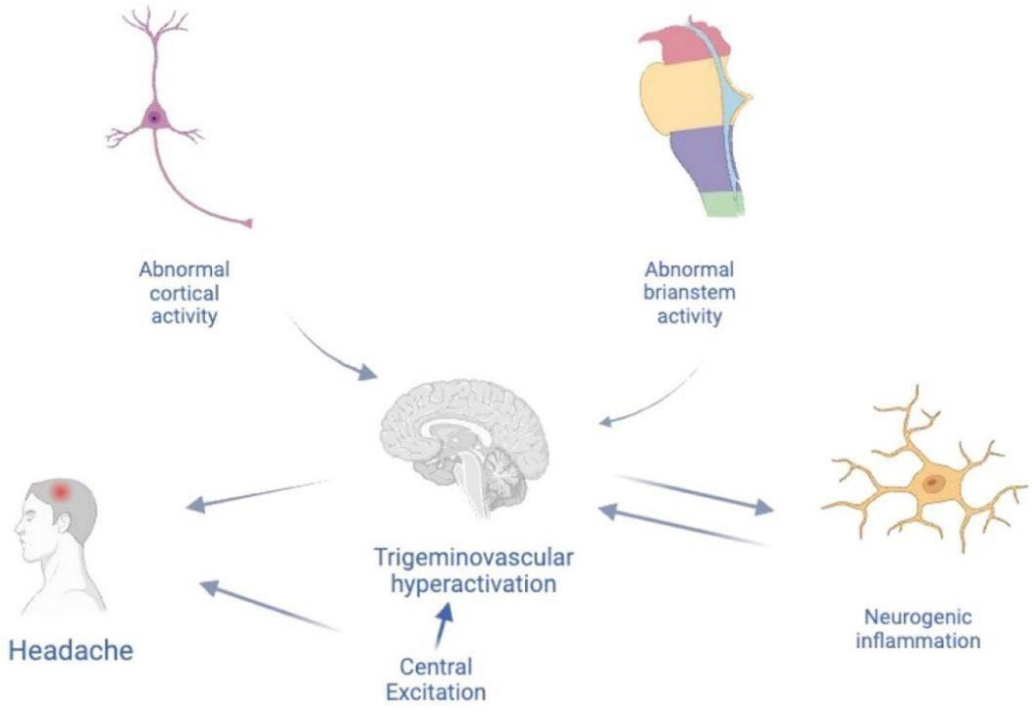

Fig no. 2 Pathophysiology of Migraine

TYPES OF MIGRAINE: -

The Third Edition of the International Classification of Headache Disorders (ICHD-3) categorizes migraines into two main types: episodic migraine (EM) and chronic migraine (CM). Chronic migraine is defined as experiencing headaches on at least 15 days per month, with migraine-like symptoms—such as throbbing pain, nausea, or sensitivity to light—occurring on at least 8 of those days for a duration of three consecutive months. This condition impacts approximately 1% to 2% of the overall population and represents about 8% of all individuals diagnosed with migraines. Furthermore, it is noteworthy that 3% of those with episodic migraine (EM) transition to chronic migraine each year.

Chronic migraine imposes a burden on healthcare systems and patients' quality of life that is four times greater than that of episodic migraine. Various risk factors play a role in the onset of chronic migraine, such as older age, being female, lower educational attainment, and the excessive use of acute migraine treatments, a condition referred to as medication overuse headache (MOH). Migraine is classified as a primary headache disorder and is primarily categorized into two forms: migraine with aura and migraine without aura.

Migraine with aura, previously known as classical migraine, is defined by the presence of sensory and/or neurological disturbances, referred to as the aura, that occur prior to the headache. These disturbances may manifest as visual anomalies, such as flashing lights or blind spots, as well as sensory issues like tingling or numbness in the face or extremities. The headache phase typically follows the aura, which can last between 20 to 60 minutes. In contrast, migraine without aura, formerly termed common migraine, is the most common type, characterized by the occurrence of headaches without any preceding aura symptoms. This variant constitutes the majority of migraine cases. Chronic migraine, a specific subtype, is sometimes called high frequency episodic migraine. This condition is identified by experiencing 15 or more headache days each month, with at least 8 of those days exhibiting migraine-like symptoms lasting over a period of 3 months. Chronic migraine often signifies a transition from episodic migraine to a more enduring and debilitating state.

MIGRAINE WITH AURA	MIGRAINE WITHOUT AURA

Visual, sensory and speech disturbances	**The duration of migraine ranging from 4 to 72 hours**
Headaches may start with aura	**Severe headache localised to one side**
Diagnosis may be mistaken for sinusitis or typical headache	**Daily routine may involve progressively worsening headache**
Could be confused with ischemic attack or occipital epilepsy	**Often accompanied by gastrointestinal symptoms**
Intracerebral arterial vasoconstrictions	**A neurobiological condition**

DIAGNOSIS: -

The diagnosis of migraine headaches is predominantly based on clinical evaluation, which emphasizes the importance of gathering a comprehensive patient history and performing an extensive examination of the central nervous system (CNS). A critical aspect of diagnosing migraines is the patient's capacity to articulate the complete spectrum of their symptoms. A detailed medical history is essential for accurate diagnosis, while the primary objective of the physical examination is to uncover any additional factors that may heighten the patient's likelihood of experiencing migraines. In many instances, the patient history alone suffices for diagnosing migraine headaches, assuming the appropriate questions are posed. Patients generally report a history of unilateral, throbbing headaches that typically initiate in the supraorbital region and subsequently extend to the temporal area. This discomfort is frequently accompanied by symptoms such as nausea, vomiting, and heightened sensitivity to light (photophobia) and sound (phonophobia). In chronic cases, migraines may occur as frequently as two to three times per week.

Additionally, patients often express frustration or discouragement due to the failure of multiple previous treatments. This sense of discouragement can stem from the fact that earlier treatments may have been ineffective, or their migraines may have gone underdiagnosed due to a hastily obtained or superficial history. A thorough and patient-centered approach to gathering the medical history is essential for accurately diagnosing and managing migraine, as overlooking key symptoms can lead to misdiagnosis and ineffective treatment.

TREATMENT OF MIGRAINE: -

The main goals of migraine treatment are to reduce the intensity of pain during an attack and prevent future attacks. Prophylactic treatment is crucial for patients with chronic migraines, while patients with acute migraines may benefit from symptom-oriented therapies due to the lower frequency of their attacks.

Treatment for migraines is usually divided into two main categories: acute treatment, which aims to stop an active migraine attack, and prophylactic treatment, which is recommended to reduce the frequency and severity of attacks over time.

Acute Treatment:

The acute treatment aims to relieve headache and associated migraine symptoms within two hours of the onset of an attack. Medications used in acute treatment can be classified into several categories:

- Analgesics and Non-Steroidal Anti-inflammatory Drugs (NSAIDs)
- Triptans (serotonin receptor agonists)
- Gepants (CGRP receptor antagonists)
- Ditans (serotonin 5-HT1F receptor agonists)
- Ergot alkaloids

The choice of medication depends on factors such as the migraine characteristics of the patient (e.g., frequency, severity, and associated symptoms) and any previous treatment failures. Acute therapies typically provide rapid relief and are preferred for their fewer side effects compared to preventive treatments.

Prophylactic Treatment:

Prophylactic treatment aims to reduce the frequency and severity of migraine attacks in patients who have more than two migraine days per month. Medications commonly used in prophylactic therapy include:

- Antihypertensives (e.g., beta-blockers)
- Antidepressants (e.g., nortriptyline)
- Anticonvulsants (e.g., sodium valproate, topiramate)
- Calcium channel blockers (e.g., flunarizine, verapamil)

Among these, topiramate and onabotulinumtoxin A (Botox) have shown proven efficacy in chronic migraine management. However, preventive treatments are often limited by their low effectiveness, side effects, and low tolerability in some patients.

Non-Pharmacological Treatments:

In addition to pharmacological approaches, non-pharmacological treatments are frequently employed either as stand-alone therapies or as adjuncts to medications. These treatments can be highly effective in managing migraine, particularly when combined with drug therapies. Some of the most effective non-pharmacological treatments include:

- Cognitive Behavioural Therapy (CBT)
- Biofeedback therapy
- Relaxation training

Other less effective options include:

- Physical therapy
- Sleep management
- Acupuncture
- Dietary regulation

While these approaches may not directly replace medications, they can minimize drug use and offer a multidisciplinary approach to migraine management, improving overall treatment outcomes and quality of life for patients.

NEW ANTI-MIGRAINE DRUGS: -

Many drugs that are FDA-approved for other conditions have also been found effective for treating acute and preventive migraine attacks. Over time, as our understanding of the migraine mechanism has evolved, additional medications have been repurposed or developed specifically for migraine management. Some of the most commonly used medications to treat migraines include ergot alkaloids, valproate, topiramate, β blockers, calcium channel blockers, and amitriptyline.

Analgesics:

Paracetamol (acetaminophen) and NSAIDs (nonsteroidal anti-inflammatory drugs) such as ibuprofen, aspirin, diclofenac, and naproxen are typically the first-line treatment for acute migraine due to their analgesic properties. These drugs are effective in providing pain relief, with paracetamol often used in combination with NSAIDs to manage mild to moderate migraine pain. However, paracetamol alone is generally not recommended as the first treatment choice.

Among NSAIDs, naproxen is the least effective in terms of speed and required dosage, often necessitating higher doses to achieve adequate pain relief. If analgesics fail to control the pain, triptans are generally recommended as a next step. It is important to mention that although analgesics were originally approved to treat other conditions, their use to treat migraines was later approved by the FDA.

Triptans:

Triptans are considered the gold standard in the treatment of acute migraine attacks and are specific medications for migraines. They are often used for moderate to severe headaches, but show the greatest effectiveness when taken in the early stages of a migraine, ideally at the beginning of the headache when symptoms are still mild.

The mechanism of action of triptans is based on increasing serotonin signaling by stimulating the 5-HT1B/1D receptors on the blood vessels and nerve endings of the skull. This activation results in the constriction of blood vessels, which counteracts the vasodilation that occurs during a migraine attack. In addition, triptans inhibit the release of neuropeptides associated with migraines, such as calcitonin gene-related peptide (CGRP) and substance P, both of which play a role in the pain and inflammation associated with migraines.

Due to their vasoconstrictor effects, triptans may carry a risk of cardiovascular side effects, particularly in patients with underlying heart disease or risk factors for cardiovascular events. These potential side effects must be considered when prescribing triptans, particularly for patients with a history of cardiovascular disease.

DRUGS: -

1. Sumatriptan
2. Zolmitriptan
3. Naratriptan
4. Rizatriptan
5. Almotriptan
6. Frovatriptan
7. Eletriptan
8. Lasmitidan

6.3 CGRP-Dependent Therapies:

CGRP (Calcitonin Gene-Related Peptide) is a peptide with 37 amino acids that plays an essential role in the pathophysiology of migraine. It acts as a powerful vasodilator in various vascular tissues and is particularly effective in the trigeminovascular system, which plays a central role in the development of migraine attacks. During a migraine attack, CGRP levels in the blood rise, especially during a chronic migraine attack, making CGRP a potential biomarker for chronic migraine.

Therapies targeting the CGRP pathway are categorized into monoclonal antibodies and small-molecule drugs. Both approaches are designed to block the CGRP receptor or inhibit CGRP itself, as both the peptide and its receptor are present in the peripheral and central parts of the trigeminovascular pathway, where they mediate vasodilation and pain signalling.

Monoclonal Antibodies and CGRP Receptor Antagonists

Monoclonal antibodies that target CGRP or its receptor have been established as an effective therapy for the prevention of chronic migraine. However, challenges with patient compliance have been a limitation. These drugs typically require monthly or quarterly parenteral (injectable) administration, which may deter some patients from consistent use.

To overcome these barriers, the development of small-molecule CGRP receptor antagonists has gained attention. These drugs are oral and designed to block CGRP signalling at the receptor level, offering a more convenient option for patients. However, the first-generation small molecule CGRP antagonists were associated with hepatotoxicity, prompting the development of second- and third-generation drugs aimed at reducing these harmful side effects.

Effectiveness of CGRP-Dependent Therapies

In the last 25 years, targeting the CGRP pathway has shown significant success in treating migraine. Small-molecule CGRP receptor antagonists have proven to be effective for acute migraine treatment, providing rapid relief during a migraine attack. In contrast, monoclonal antibodies are primarily used for preventive treatment in chronic migraine patients, reducing the frequency and severity of attacks over time.

6.3.1. Anti-CGRP Monoclonal Antibodies:

Due to the side effects and limitations of currently available migraine medications, there is an ongoing need to explore new classes of drugs. In 2018, monoclonal antibodies (mAbs) targeting the CGRP receptor emerged as a significant advancement in migraine treatment. These large molecule drugs have become a cornerstone in migraine prophylaxis, offering a targeted approach to reducing the frequency and severity of migraine attacks. The introduction of mAbs represents an important milestone in the development of safer and more effective treatments for patients with chronic migraine, addressing some of the limitations associated with traditional migraine therapies.

- Erenumab
- Galcanezumab
- Fremanezumab
- Eptinezumab

6.3.2. Gepants:

The discovery of gepants has introduced a new perspective in migraine treatment, offering significant advantages over traditional therapies. These CGRP receptor antagonists have proven to be safer than triptans, with no significant hepatotoxicity or cerebrovascular side effects reported. Gepants are effective in both acute and prophylactic treatments, providing relief from migraine pain within 2 hours and significantly reducing the frequency of attacks.

In addition to their safety profile, gepants are particularly suitable for use during pregnancy compared to other migraine treatments, including monoclonal antibodies (mAbs). Gepants also offer greater ease of use, as they are typically oral medications, making them a more convenient option for patients compared to the injectable mAbs.

- Ubrogepant
- Rimegepant
- Zavegepant
- Atogepant

DRUG–DRUG INTERACTIONS OF NEW ANTI-MIGRAINE DRUGS: -

Drug-Drug Interactions (DDIs) during the pharmacokinetic phase can have a profound impact on the blood concentration and bioavailability of a drug, ultimately influencing its safety and efficacy. In addition, pharmacodynamic interactions, where drugs act as either agonists or antagonists at specific receptors, can modify the therapeutic effects— either enhancing or diminishing them. The likelihood of a drug interaction increases as more medications are introduced. When two drugs are taken together, the risk of a clinically significant interaction is already present. If seven or more drugs are used concurrently, the likelihood of an interaction becomes nearly certain.

A. Lasmiditan:

- Lasmiditan, the first drug in the ditan class, was approved by the U.S. Food and Drug Administration (FDA) in October 2019 for the acute treatment of migraine, with or without aura, in adults.
  The available doses are 50 mg and 100 mg tablets.

- Lasmiditan is chemically 2,4,6-trifluoro-N-[6-(1methylpiperidine-4-carbonyl) pyridin-2-yl] benzamide.
- Lasmiditan acts as an agonist of the 5-HT receptor and shows a binding affinity to the 5-HT1F receptor that is more than 440 times stronger than the affinity for the 5-HT1B and 5-HT1D receptors. This strong binding helps to inhibit the electrical stimulation markers in the trigeminal ganglion.
- By inhibiting the release of neuropeptides such as CGRP and glutamate, lasmiditan disrupts the migraine pain pathways, preventing their local activity and reducing the intensity of a migraine attack.
- The efficacy and safety of lasmiditan in stopping migraine attacks has been confirmed in randomized phase III trials, which showed positive results compared to placebo. These studies also included patients with vascular risk factors. Because lasmiditan targets the 5-HT1F receptor, which is predominantly found in the trigeminal nerve and not in vascular smooth muscle (like the 5-HT1B and 5-HT1D receptors), it does not cause vasoconstriction. This makes it a safer option for patients with cardiovascular diseases, unlike triptans.
- Lasmiditan is absorbed quickly and reaches the highest plasma levels after about 1.8 hours.
- Studies have found that there is no significant difference in the absorption and bioavailability of lasmiditan, regardless of whether it is taken during a migraine attack or in the interictal phase.
- Taking lasmiditan with a high-fat meal may delay the time to reach maximum plasma concentration (Tmax) by about an hour and increase the maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) by 22% and 19%, respectively.
- Lasmiditan binds to blood proteins to a degree of 55%-60%, with a half-life ($T_{1/2}$) of around 5.7 hours.
- No drug accumulation occurs with daily administration of lasmiditan.
- Renal excretion plays only a minor role in the clearance of lasmiditan.
  The drug is primarily metabolized by non-cytochrome P450 (CYP) enzymes in both the liver and extrahepatic tissues.
- The following enzymes play no role in metabolism: monoamine oxidase, CYP450 reductase, xanthine oxidase, alcohol dehydrogenase, aldehydrogenase and aldoketoreductase.
- Only about 3% of the administered dose of lasmiditan is excreted unchanged in the urine.
- Lasmiditan has not been studied in patients with severe hepatic insufficiency, and its use is not recommended in such cases.
- The recommended dosage of lasmiditan is between 50 mg and 200 mg, depending on the severity of the migraine headache.
- It is advised that patients do not take more than one dose of lasmiditan per day and avoid driving for up to 8 hours after taking the medication.
- Common side effects include dizziness, fatigue, paraesthesia, and sedation.
- In combination with propranolol, a single dose of 200 mg lasmiditan was found to increase heart rate by an additional five beats per minute in healthy volunteers, with an average maximum increase of 19 beats per minute compared to propranolol alone.
- The combined administration of lasmiditan with alcohol or CNS depressants has not been extensively studied in clinical trials. However, given that lasmiditan may cause sedation and other cognitive or neuropsychiatric adverse effects, caution should be exercised when used alongside alcohol or CNS depressants.
- Lasmiditan is highly lipophilic, allowing it to cross the blood brain barrier (BBB). As a result, central nervous system (CNS)mediated side effects like somnolence and fatigue are the most commonly observed adverse effects.
- Clinical studies show that lasmiditan has no effect on the pharmacokinetics of midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 substrate), tolbutamide (a CYP2C9 substrate), sumatriptan, propranolol or topiramate.

In summary, lasmiditan and its metabolites do not significantly inhibit or induce the major CYP enzymes, making them clinically irrelevant for interactions with these enzymes.

B. Gepants:

i) Ubrogepant

- Ubrogepant was the first gepant approved by the FDA in December 2019 for the acute treatment of migraine, with or without aura, in adults.
- Chemical structure of ubrogepant:
- The recommended oral dose of ubrogepant is 50 mg or 100 mg, depending on the severity of pain. A maximum of two doses may be taken per day, with at least 2 hours between doses.
- The maximum daily dose is 200 mg.
- Clinical studies have confirmed ubrogepant's efficacy and good tolerance in comparison to a placebo.

- Ubrogepant is rapidly absorbed after oral administration.
- Common side effects are rare, but include nausea, insomnia, dry mouth, and the potential for hepatotoxicity should be considered.
- The pharmacokinetics of ubrogepant is dose-proportional within the range of 1 mg to 400 mg. There is no accumulation after multiple daily doses, and steady-state is typically achieved within 2 days.
- Factors such as age, sex, race, body weight, and mild to moderate renal and hepatic impairment do not significantly affect the pharmacokinetics (e.g., AUC and Cmax) of ubrogepant.
- For a single oral dose, the mean apparent central volume of distribution of ubrogepant is approximately 350 L.

ii) Rimegepant

- Ubrogepant and rimegepant are part of the new generation of oral gepants that have received FDA approval for acute migraine treatment.
- Rimegepant is an oral CGRP receptor antagonist developed by Biohaven Pharmaceuticals. It was approved by the FDA on February 27, 2020, for the acute treatment of migraine.
- Indications: Rimegepant is approved for the acute treatment of migraine (with or without aura) in adults and for the prevention of episodic migraines in adults.
- Mechanism of Action: Rimegepant works by blocking the action of CGRP, a pronociceptive molecule implicated in the pathophysiology of migraine, thus helping to abort migraine headaches.
- Hepatic Considerations: Clinical trials have shown that rimegepant plasma concentrations are significantly higher in patients with severe hepatic impairment (e.g., Child-Pugh C). It should not be used in this population.
- Hypersensitivity Reactions: Some patients have experienced hypersensitivity reactions during clinical trials. If such reactions occur, rimegepant should be discontinued immediately.
- The oral bioavailability of rimegepant is approximately 64%. After administration of the orally disintegrating tablet, the maximum plasma concentration (C_{max}) is reached at around 1.5 hours (T_{max}).
- Food Interactions: When taken with a high-fat meal, the T_{max} is delayed by about 1 hour, while Cmax decreases by 42-53%, and AUC is reduced by 32-38%. We do not yet fully understand the therapeutic significance of these changes.
- At steady state, the volume of distribution for rimegepant is approximately 120 L.
- Metabolism: Rimegepant is primarily metabolized by CYP3A4, with some contribution from CYP2C9. No specific metabolites have been identified, and no major metabolites have been detected in plasma.
- In the case of overdosage, there is no specific antidote for rimegepant. Treatment should be symptomatic and supportive, including monitoring vital signs. Haemodialysis is unlikely to be beneficial due to the high serum protein binding of the drug.

C. CGRP receptor monoclonal antibodies:

i. Erenumab

- Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody that binds to calcitonin gene related peptide (CGRP) precisely and with high affinity.
- It was developed using recombinant DNA technology in Chinese hamster ovary (CHO) cells.
- The antibody has an estimated molecular weight of 150 kDa, consisting of two heavy chains (each containing 456 amino acids) and two light chains (each containing 216 amino acids).
- Erenumab works by competitively blocking CGRP and inhibiting its function. This blockade prevents the activation of adenylate cyclase, reducing cAMP accumulation, a process demonstrated in both in vivo and in vitro studies.
- In in vitro studies, erenumab demonstrated potent and competitive inhibition of the binding of [125I]-CGRP to the canonical CGRP receptor, fully inhibiting the CGRP induced cAMP accumulation in human SK-N-MC neuroblastoma cells.

Mechanism of Action of Erenumab:

- Erenumab competitively blocks the CGRP receptor by antagonizing the functions of CGRP receptor
- Erenumab is administered subcutaneously, with a typical dosage of 70 mg once a month. For some patients, a dose of 140 mg per month is higher and may be beneficial. The injection is injected into the abdomen, thigh, or upper arm.
- According to population pharmacokinetic analysis, the drug's pharmacokinetics are not significantly influenced by factors such as age, gender, race, or whether the patient has episodic or chronic migraine. However, there is insufficient evidence regarding its pharmacokinetics in specific patient subgroups.
- Erenumab has not been studied in patients with severe renal impairment (eGFR <30 ml/min/1.73m²).
- The use of erenumab in patients with hepatic impairment has not been studied. As a human monoclonal antibody, erenumab is not metabolized by cytochrome P450 enzymes, and hepatic clearance is not an excellent pathway for the elimination of the drug.

ii. Galcanezumab

- Galcanezumab is a humanized monoclonal antibody developed by Eli Lilly and Company to target calcitonin gene-related peptide (CGRP).
- While several small-molecule CGRP receptor antagonists have been introduced, galcanezumab is specifically engineered to selectively bind to CGRP with high affinity and potency.
- Approved by the FDA in September 2018, galcanezumab is indicated for preventive migraine treatment and episodic cluster headache management.

- A pregnancy exposure registry has been established to monitor the safety of galcanezumab in pregnant women.
- Galcanezumab is administered via subcutaneous injection.
- Clinical trials have demonstrated that galcanezumab significantly reduces the average number of migraine headache days and is well-tolerated by patients.
- Some galcanezumab patients have experienced hypersensitivity events, including rash, urticaria, and dyspnea.
- Galcanezumab works by binding to endogenous CGRP, preventing its interaction with CGRP receptors and interfering with its migraine-promoting activity.
- Research has shown that intravenous CGRP administration can provoke migraine-like attacks in patients with a history of migraines, emphasizing the importance of blocking CGRP in migraine prevention.
- Humanized monoclonal antibodies like galcanezumab have shown promising results in reducing the frequency of migraine attacks during early clinical trials.
- The apparent volume of distribution for galcanezumab is 7.3 L, with a 34% inter-individual variability.
- Following administration, galcanezumab undergoes proteolysis, breaking down into smaller peptides and amino acids, similar to the metabolism of endogenous immunoglobulins.
- Galcanezumab is not metabolized by liver enzymes, reducing the likelihood of drug-drug interactions.

FUTURE DIRECTIONS OF PHARMACOLOGICAL MANAGEMENT OF MIGRAINE:

Several innovative therapies are currently under investigation, spanning a wide range of approaches, including trigeminovascular therapies, cannabis-based treatments, hormonal and metabolic interventions, and other emerging options.

Trigemino-vascular Therapies:

- Neuropeptides and G protein-coupled receptors involved in the Trigemino-vascular system are key targets for reducing neurogenic inflammation, vasodilation, and pain transmission that are central to migraine pathophysiology.
- Activation of sensory fibres within the trigeminal nerve releases various peptides, such as pituitary adenylate cyclase-activating polypeptide (PACAP), which play a significant role in neurogenic inflammation and pain sensitization.
- Meningeal mast cells (MCs), which are in close proximity to trigeminal nerve endings, release histamine that stimulates nociceptors. This release further activates the mast cells, creating a vicious cycle that exacerbates migraine pain.
- Lu AG09222 is a monoclonal antibody specifically designed to inhibit PACAP, and a proof-of-concept study in healthy volunteers demonstrated that it could prevent PACAP38induced cephalic vasodilation and headache, supporting its potential in migraine prevention.
- LY 3451838 is another monoclonal antibody targeting PACAP. It has been tested in a phase II trial (NCT04498910) in patients who had not responded to two to four prior prophylactic migraine treatments.
- Histamine, a known migraine trigger, likely acts through H1 and H3 receptor subtypes. AGX-201 is a histamine receptor modulator that targets both H1 receptors (as an antagonist) and H3 receptors (as an agonist), offering a novel way to mitigate migraine symptoms by reducing the release of proinflammatory neuropeptides.

Cannabis-Based Therapies:

- The growing interest in cannabis-based treatments for migraine is driven by patient-reported benefits in both acute and preventive settings.
- Cannabinoid receptors, primarily CB1 and CB2, are abundant in both the central and peripheral nervous systems. These receptors are essential in modulating pain transmission, inflammation, and vascular regulation—all of which contribute to migraine development.
- Cannabinoids, the active compounds in cannabis, interact with these receptors to exert various effects: CB1 receptor activation in the CNS reduces pain signaling, while CB2 receptor activation on immune cells helps to alleviate inflammation linked to migraines.
- A study sponsored by the University of Calgary is set to begin in 2024 to further explore the potential of cannabis in migraine treatment. However, challenges such as the long-term safety of cannabis use, dependence risks, and legal concerns highlight the need for further, thorough clinical investigations.

Hormonal and Metabolic Therapies:

- Emerging research indicates that hormonal and metabolic pathways may play a pivotal role in migraine pathophysiology, offering new therapeutic targets.
- Oxytocin, a neuropeptide involved in childbirth and lactation, has shown promise in pain modulation. Fluctuations in oxytocin levels during migraine attacks suggest that its dysregulation may contribute to the onset of migraines.

- Sepranolone (also known as isopregnanolone) is a neuroactive steroid that modulates the GABAA receptor. There is growing evidence that neurosteroids can influence nociceptive and neuropathic pain, making them a potential tool for migraine treatment.
- A proof-of-concept study on sepranolone has investigated its efficacy in preventing menstrual migraines in women. Conducted across three European countries (Denmark, Finland, and Sweden), the results are being evaluated and have been submitted to ClinicalTrials.gov.
- Tricaprilin is under investigation for its potential applications in Alzheimer's disease and infantile spasms, with possible implications for migraine therapy.

Other Therapies:

- While analgesics are the mainstay of acute migraine treatment, a single analgesic may not always provide sufficient relief. As a result, there is ongoing exploration of combination therapies that incorporate multiple agents to enhance efficacy.
- AXS-07 is an investigational oral therapy composed of meloxicam and rizatriptan. This combination is designed to increase the absorption rate of meloxicam, offering an enhanced treatment option for the acute management of migraines, with or without aura.
- Prabotulinumtoxin A, currently being studied for migraine prevention, is being tested in adults who experience six or more migraine days per month, offering a potential new option for patients with chronic migraine.

CONCLUSION: -

Migraine headaches represent a widespread and often disabling condition that demands a comprehensive diagnostic and treatment strategy. *Diagnosis* is primarily based on the patient's detailed medical history, with an emphasis on identifying hallmark symptoms such as unilateral, throbbing pain, often accompanied by nausea, vomiting, and heightened sensitivity to light and sound. Understanding the full spectrum of a patient's symptoms is key to accurate diagnosis and effective treatment. A thorough history allows clinicians to distinguish migraines from other potential causes of headache, reducing the risk of misdiagnosis.

When it comes to *treatment*, the goals are twofold: *acute management* to address pain and other symptoms during an active migraine, and *preventive strategies* aimed at reducing the frequency and severity of future episodes. For acute attacks, medications like NSAIDs, triptans, gepants, and ergot alkaloids are used based on the individual patient's migraine pattern and response to previous treatments. On the preventive side, patients who experience frequent migraines benefit from therapies such as antihypertensives, anticonvulsants, and antidepressants, with newer options like CGRP inhibitors and Botox showing promise for chronic migraine sufferers.

Beyond medications, *non-pharmacological treatments* have proven effective, particularly when combined with medical therapies. Approaches like cognitive behavioural therapy (CBT), biofeedback, and relaxation techniques offer complementary benefits by helping patients manage stress and reduce migraine triggers. While not a replacement for medication, these strategies can reduce the need for drugs, improve patient well-being, and contribute to more sustainable long-term management.

Ultimately, *effective migraine care* involves a personalized, multidisciplinary approach that integrates both pharmacological and non-pharmacological treatments. Regular monitoring, patient education, and a focus on managing triggers and comorbidities are essential to optimizing care and improving the quality of life for those affected by this challenging condition. With a comprehensive, patient-centered strategy, migraines can be better controlled, allowing individuals to regain control over their daily lives.

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