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# MIGRAINE THERAPY: CURRENT AND EMERGING TREATMENT STRATEGIES

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**Abstract**
Migraine is a chronic, recurrent neurological disorder characterized by moderate to severe headache attacks often associated with nausea, vomiting, photophobia, and phonophobia. It affects approximately 15% of the global population and significantly impairs quality of life, work productivity, and social functioning. Migraine is classified into migraine with aura and migraine without aura, with varying pathophysiological mechanisms. Recent advances in understanding migraine neurobiology-particularly the role of calcitonin gene-related peptide (CGRP)-have transformed treatment strategies. Traditional therapies such as NSAIDs, triptans, and ergot derivatives remain widely used; however, newer therapies including CGRP monoclonal antibodies, gepants, and ditans have expanded therapeutic options. This review provides a comprehensive overview of migraine types, risk factors, pathophysiology, pharmacological and non-pharmacological treatments, newly approved therapies, limitations, challenges, and future strategies in migraine management.
***Keywords:*** *Migraine, CGRP antagonists, Triptans, Preventive therapy, Acute treatment, Monoclonal antibodies.*



## INTRODUCTION

Migraine is a complex neurovascular disorder recognized as one of the leading causes of disability worldwide. According to the World Health Organization, migraine ranks among the top neurological disorders contributing to years lived with disability.

Clinically, migraine presents as unilateral, pulsating headache lasting 4–72 hours and may be aggravated by physical activity. It is frequently accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia) [1].

Migraine is broadly classified into:

- Migraine without aura (MO)
- Migraine with aura (MA)

Recent research has shifted from the traditional vascular theory to the neurovascular and trigeminovascular hypothesis, emphasizing the role of neurotransmitters such as CGRP, serotonin (5-HT), and PACAP [2].

## TYPES OF HEADACHE

Headaches are broadly divided into primary and secondary types.

1. Primary Headaches
    - Tension-type headache
    - Migraine
    - Cluster headache
    - Hemicrania continua
    - Ice-pick headache
2. Secondary Headaches
    - Sinus headache
    - Hypertension headache
    - Post-traumatic headache
    - Spinal headache
    - Thunderclap headache

Among these, migraine remains the most disabling.

1.1. Risk factors

Major risk factors include:

- Genetic predisposition
- Hormonal changes (menstrual cycle, pregnancy)
- Stress
- Sleep disturbances
- Obesity
- Medication overuse
- Caffeine withdrawal

Medication Overuse Headache (MOH) occurs when acute medications are used excessively, leading to chronic daily headaches.

1.2. Stigma and impact on the individual

Important Effects of Stigma on Specific Patients:

Internalised Stigma: People with chronic migraine often internalise the negative attitudes of society, leading to feelings of inadequacy, humiliation, and a diminished sense of self efficacy in managing their condition. Delayed Treatment Seeking: When patients

believe their pain is not "serious" or will be disregarded, they delay seeking professional medical help. Implications for Mental Health: Stigma is linked to higher levels of anxiety, depression, and social isolation-all of which are frequently triggered by migraines [3].

**Impact on Migraine Management and Treatment**

Suboptimal Care: Only 15% to 26% of European patients seek professional advice for headaches, resulting in a low uptake of preventative interventions, partly because of a fear of shame. Healthcare Disparities: Patients may be discouraged from scheduling crucial follow-up consultations in emergency rooms by being labelled as "dramatic" or "drug-seeking." Reduced Research Funding: Social stigma contributes to the lower federal funding for research as compared to other neurological conditions [4].

## 2. Mechanism of Action of Antimigraine Drugs

Although the precise cause of migraine is uncertain, several theories have been put forth, including vascular dysfunction, magnesium deficiency, and an aseptic inflammatory response in the dura mater (Figure 1 A, B, C) When these stimuli cause the trigeminal nerve system to become sensitised, the trigeminal ganglion (TG) releases a variety of neuropeptides, including substance P (SP), CGRP, and pituitary adenylate cyclase activating polypeptide (PACAP), to aid in the neuroinflammatory response(5). Additionally, because TGVS is in a chronically activated state, it causes a number of additional alterations, such as changes in meningeal vasodilation and mast cell degranulation. More intriguingly, CSD can change the blood–brain barrier's permeability by activating and upregulating matrix metalloproteinases (6). Given that CGRP is a crucial peptide involved in pain signaling, it has been shown that utilizing herbs can suppress the release of CGRP. For patients who are insensitive to CGRP antagonists, PACAP antagonists might be a novel treatment alternative [7].

## 3. MIGRAINE PAIN THEORIES

The precise process by which migraines are produced is not fully known. According to the vascular theory, the migraine's associated discomfort was caused by extracranial vasodilation after intracerebral artery vasoconstriction. This theory was refuted, and research by Amin et al. suggested that extracranial artery dilatation was not likely to be a factor in migraines The neurovascular hypothesis is the currently recognized explanation for migraine headaches. This theory suggests that migraine pain originates in the trigemino vascular system, which helps nociceptive impulses travel from the meningeal blood vessels to higher regions of the central nervous system [8]. When the trigeminal sensory nerves are activated, vasoactive neuropeptides such substance P, neurokinin A, and CGRP are produced. These vasoactive neuropeptides cause dural plasma extravasation and vasodilation, which results in neurogenic inflammation. The trigeminal nucleus caudalis receives pain impulses via the trigemino vascular system, which then sends them to the brain's higher cortical pain regions.

## ACUTE TREATMENT OF MIGRAINE

When patients are able to identify their headache and the drug that is most likely to help them, a stratified therapy approach is optimized. For mild to moderate to severe migraines, patients should be prescribed medication [9].

1. Simple Analgesics

Numerous clinical investigations have shown that aspirin, paracetamol (acetaminophen), and other NSAIDs are effective in treating migraine attacks. Patients who cannot tolerate NSAIDs are the main beneficiaries of paracetamol, which is less effective [10].

2. Triptans

5-HT1B/1D receptor agonists, or triptans, are utilized as second-line treatments when basic analgesics are insufficient to relieve headaches. Second -line therapy for moderate-to-severe migraine [11].

3. Antiemetics

Simple analgesics or triptans can be used in conjunction with antiemetics to treat nausea and vomiting associated with migraines; however, there is no proof that antiemetics enhance the absorption of anti-migraine medications [12].

## PREVENTIVE TREATMENT

Patients whose quality of life is negatively impacted by migraines, even after receiving the best acute treatment, should be offered preventive pharmacological migraine medication. Patients who experience at least four migraine days each month are eligible for such treatment.

1. Antihypertensive drugs

Clinical experiments have demonstrated the effectiveness of certain β-blockers when compared to a placebo. The outcomes of these studies, which were mostly carried out in the 1980s, are constrained by their short duration, poor methodological quality, and potential for publication bias [13]. Dizziness, weariness, and cold extremities are the most frequent adverse effects.

2. Antiepileptics

Although topiramate and valproate are linked to more negative side effects, their established efficacy is comparable to that of β-blockers [14].

3. Antidepressants

Amitriptyline is a tricyclic antidepressant medication that is frequently used to prevent migraines. Patients who also frequently get tension-type headaches are thought to benefit from it [15].

4. Calcium Channel Blockers

In order to decrease the frequency of attacks, calcium channel blockers (CCBs), including verapamil and flunarizine, are used as second-line, off-label preventive therapies for chronic migraine [16]. These medications

function as vasodilators to treat migraines by preventing calcium from entering vascular smooth muscle and preventing cerebral vasospasm. In general, people with concomitant hypertension benefit from them.

5. Botulinum Toxin A

Action Mechanism: By acting on sensory nerves, the toxin prevents the release of neurotransmitters that are involved in pain signalling, such as CGRP.

## DRUGS TARGETING THE 5-HT SYSTEM

5-HT is a nonvascular serotonergic non-triptan receptor that has no effect on cerebral microvascular smooth muscle, in contrast to 5-HT and 5-HT that the triptans target. This implies that 5-HT is not involved in the vasoconstriction of the human brain's microcirculation. Therefore, for individuals with CVD who are unable to take triptans, it might be an option [17].

## CGRP AS A TREATMENT TARGET

Both central and peripheral neurons contain the CGRP receptor. In migraineurs, exogenous CGRP can result in both acute headaches and delayed migraine-like events (42). While CGRP mAbs are large-molecule CGRP receptor or ligand antagonists, gepants, ubrogepant, and rimegepant are small-molecule CGRP receptor antagonists (18).

## NEWLY APPROVED AND EMERGING TREATMENT OPTIONS

Three CGRP mAbs-erenumab, fremanezumab, and galcanezumab-were authorized by the FDA in 2018 to prevent adult migraines. All of them are given monthly subcutaneously (SC), with fremanezumab receiving an extra quarterly dosage schedule [19]. Injection-site responses brought on by the SC administration are the most frequent side effects.

## SELF TREATMENT AND DIAGNOSTIC DELAY

Self-treatment and delayed diagnosis are prevalent issues in migraine treatment, with many people waiting years to have a formal diagnosis. A high frequency of drug overuse headaches and, in certain situations, the development from episodic to chronic migraines are caused by patients' prolonged dependence on over-the-counter (OTC) medications [20].

## TREATMENT LIMITATIONS

Treatment options for migraines are frequently constrained by moderate efficacy, side effects, contraindications, and tolerance concerns [21]. Acute medication-overuse headaches (MOH), delayed preventive action (up to 12 weeks), poor patient adherence, high expenses, and inadequate alleviation (non-response) for many patients-which frequently necessitates drug switching-are common drawbacks.

## CHALLENGES

Significant obstacles to treating migraines include low preventive care utilisation, underdiagnosis, and high rates of ineffective over-the-counter pharmaceutical self medication [22]. Medication overuse headaches (MOH), restricted access to experts, sluggish adoption of novel treatments such as CGRP inhibitors, and the requirement for highly customised procedures are some of the main challenges [23].

## FUTURE STRATEGIES

With cutting-edge CGRP/PACAP-targeting treatments, non-invasive neuromodulation tools (vagus nerve, magnetic stimulation), and digital therapies like virtual reality, migraine therapy approaches are moving toward precision medicine. In order to monitor and lower the frequency of attacks, future strategies will integrate lifestyle modifications, metabolic/hormonal management, and smart wearable technology with individualised treatment.

## CONCLUSION

Migraine is a multifactorial neurological disorder requiring individualized treatment strategies. While traditional therapies such as NSAIDs and triptans remain important, newer therapies targeting CGRP pathways have significantly transformed migraine management. Monoclonal antibodies, gepants, and ditans offer improved safety and efficacy, particularly in patients who are non-responsive to conventional therapy. Despite advancements, challenges such as high cost, treatment resistance, and medication overuse remain. Future research focusing on precision medicine and innovative drug delivery systems promises improved outcomes for migraine patients.

The evolving landscape of migraine therapeutics marks a hopeful era for patients and clinicians alike.

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## AUTHOR CONTRIBUTIONS

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The authors declare that there are no conflicts of interest regarding the publication of this paper.

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