**Advances in Migraine Therapy: A Comprehensive Review**

**ABSTRACT**

**Background** Migraine is a prevalent and debilitating neurological disorder, affecting a significant portion of the global population, particularly women. Characterized by intense pulsating headaches, nausea, and sensory disturbances, migraines can significantly impair quality of life. Traditional treatments often offer suboptimal relief or cause undesirable side effects, necessitating the exploration of more effective and targeted therapies. **Objective** the aim of this review is to comprehensively examine recent advances in both pharmacological and non-pharmacological approaches for the treatment and management of migraines, highlighting innovations such as CGRP inhibitors, Gepants, Ditans, neuromodulation techniques, and personalized medicine. **Methods** this review synthesizes current scientific literature, clinical trial findings, and global prevalence data to evaluate emerging migraine therapies. It categorizes treatment strategies into symptomatic and preventive approaches and includes special considerations for children and women. **Results** Recent advancements have led to the development of CGRP inhibitors (e.g., erenumab, fremanezumab), oral gepants (ubrogepant, rimegepant), and ditans (lasmiditan), which demonstrate improved efficacy and safety compared to conventional treatments. Non-pharmacological innovations, including neuromodulation devices (Cefaly, TMS), cognitive behavioral therapy, and botulinum toxin injections, offer effective alternatives, especially for patients with contraindications to medications. Personalized medicine and genetic profiling are also enhancing treatment precision. **Conclusion** These innovations offer safer, more effective, and individualized options for migraine sufferers. Continued research and clinical validation are essential to further refine these therapies and improve long-term patient outcomes.

**Keywords:** Migraine, CGRP inhibitors, neurological, Gepants, Ditans

# INTRODUCTION

A migraine is characterized by very intense pulsating headaches, often accompanied by nausea, sensitivity to light and sound, and visual disturbances. Unlike the usual headaches, migraines tend to be more severe and can take several hours or even several days to pass. They normally occur in cycles and begin with signs (aura) that cause them to go into headache phase, followed by a period of fatigue once the headache phase is over. There are a number of stimuli that may precipitate migraines, such as stress, hormonal changes, food intake, and environmental stimuli. These may have significant effects on day-to-day living and productivity. Millions are affected worldwide. Managing migraines can be achieved through lifestyle modification, medication, and learning what individual triggers are.

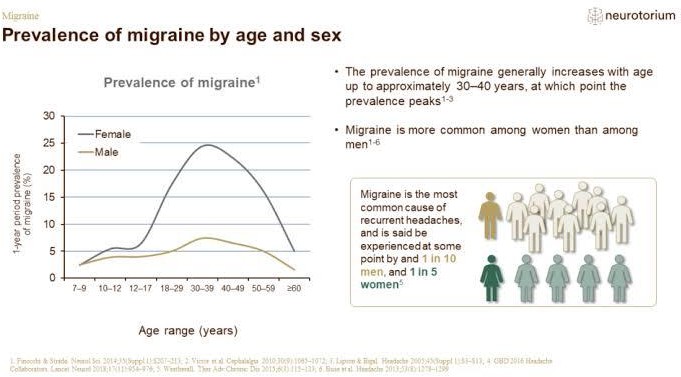
Migraine is classified as a primary headache disorder, meaning it is not caused by another medical condition. Instead, it results from abnormal neurological and vascular processes [1].

# PREVALENCE OF MIGRAINE

Migraine affects a large portion of the global population, with estimates of prevalence ranging from 12% to 15%:

Global: The 1-year prevalence of migraine is estimated at 15% worldwide. US: A 2018 survey found that 15.3% of adults in the US experience migraine or severe headache. Women vs men: Migraine is about three times more common in women than in men. In a US survey, 17.1% of women and 5.6% of men reported having migraine symptoms. Age: Migraine is most common in people aged 20 to 50 years.

Geographical regions: Prevalence varies by region, with Nepal having the highest prevalence and China having the lowest [2].



**Fig 1: Prevalence of Migraine in Global**

# TYPES OF MIGRAINE

1. **Chronic Migraine**: Refers to migraines that occur on 15 or more days per month for at least three months [3].
2. **Acute migraine: -** An acute migraine is a throbbing pain and pulsing sensation [4].

### Causes:-

* 1. Genetic Factors
* 2. Neurological Factors
* 3. Vascular Factors
* 4. Hormonal Factors
* 5. Environmental and Lifestyle Factors
* 6. Sensory Triggers
* 7. Stress
* 8. Sleep deprivation
* 9. Radiation [5][6].

**RECENT MIGRAINE THERAPY**

1. **SYMPTOMATIC THERAPY**

Symptomatic therapy for migraines focuses on relieving the immediate symptoms during a migraine attack. The primary goals are to reduce pain, alleviate associated symptoms (like nausea and sensitivity to light/sound), and restore normal functioning. Drugs used in Symptomatic Therapy

1. **Pain relievers:** Available over-the-counter is over-the-counter NSAIDs and prescription analgesics including ibuprofen and naproxen.
2. **Triptans:** Over the counter triptans selective serotonin receptor agonist and sumatriptan rizatriptan will cut headache intensity by constricting the blood vessels and inhibit pathways leading to the pain [7].
3. **Ergotamines:** DHE (dihydroergotamine), and ergotamine may be used in severe migraine as they cause constriction of the blood vessels and reduced the pain.
4. **Anti-nausea Drugs:** Metoclopramide and prochlorperazine can be used to treat nausea and vomiting related to migraine [7].

### Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

* 1. Examples: Ibuprofen, Aspirin, Naproxen.
  2. Reduces inflammation and relieved to moderate headache pain.

### Acetaminophen:

* 1. **Example:** Paracetamol.
  2. Can be used for mild headache pain; less effective for severe attacks compared to NSAIDs [8]

### Ergotamines

**Examples:** Dihydroergotamine, Ergotamine

* + **Other Adjunctive Therapies:** Cold compresses, rest, and dark, quiet environments can be added [8].

## **Acute Migraine in Children**

Mechanism: Serotonin (5-HT) receptor agonists that reduce vasodilation and neuronal sensitization in migraine**.[9]**

### Examples:

* + Sumatriptan (nasal spray, injection), Rizatriptan (oral), Zolmitriptan (nasal spray)
* **Usage:** Approved for use in children ages 6 and older, typically for moderate- to-severe migraines [10].
* **Recent Advances:** Rizatriptan has shown to be effective and safe in children, with a relatively quick onset of action, making it a preferred choice. Sumatriptan nasal spray is also used, particularly when oral administration is difficult due to nausea.

## **Triptan group of Drugs**

### Ergotamines

* **Examples:** Dihydroergotamine, Ergotamine

### Triptans

* **Mechanism:** Selective serotonin (5-HT) agonists that target 5-HT1B/1D receptors on blood vessels and trigeminal neurons.

### Examples:

* (subcutaneous, oral, nasal spray)
* Rizatriptan, Zolmitriptan, Naratriptan (oral and nasal)





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### Fig 2: Sumatriptan Injection Fig 3: Sumatriptan Tablet

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# Herbal and Nutritional Supplements in Children

* **Magnesium:** Low magnesium levels have been linked to migraines, and supplementation may help prevent attacks.
* **Riboflavin (Vitamin B2):** Studies suggest it may help reduce migraine frequency in children [11].
* **Coenzyme Q10:** This antioxidant has shown some efficacy in reducing migraine frequency [12].
* **Butterbur:** Some studies support its use for migraine prevention in children, but concerns about safety (e.g., liver toxicity) limit its us



**Fig 4: Herbal Formulation in migraine**

## **Chronic Migraine in Women**

Chronic migraine is a prevalent and disabling neurological condition, particularly affecting women. It is defined as having headaches on 15 or more days per month, of

Which at least 8 days meet criteria for migraine, for a period of three months or longer. Below is a breakdown of key aspects of chronic migraine in women:

### Triggers

Common triggers include:

* **Hormonal changes**: Menstrual cycle, pregnancy, postpartum period, and menopause.
* **Lifestyle factors**: Stress, poor sleep, dehydration, and irregular meal patterns.
* **Environmental triggers**: Weather changes, bright lights, or strong smells.
* **Dietary factors**: Caffeine, alcohol, and specific foods like aged cheeses or processed meats.(13)

### Impact on Women

* **Quality of Life**: Chronic migraines significantly impair daily activities, work productivity, and social interactions.
* **Mental Health**: Higher risk of anxiety and depression compared to episodic migraine sufferers.
* **Family and Caregiving Roles**: Balancing responsibilities with frequent debilitating headaches can add stress.

### Special Considerations for Women

* **Pregnancy**: Many preventive migraine medications are contraindicated, so non-pharmacological therapies are preferred.
* **Menopause**: Hormone fluctuations during this phase may worsen or improve migraines; individualized management is key [14].

**Calcitonin Gene-Related Peptide (CGRP) Antagonists**

CGRP antagonists have emerged as a significant breakthrough in migraine management. These medications work by inhibiting the activity of CGRP, a molecule involved in migraine pathophysiology. They are available in both injectable monoclonal antibody forms and oral formulations:

* **Injectable Monoclonal Antibodies**: Medications such as erenumab, fremanezumab, and galcanezumab are administered monthly or quarterly and have been approved for migraine prophylaxis in adults.
* **Oral CGRP Receptor Antagonists (Gepants)**: Drugs like ubrogepant and rimegepant are used for acute migraine treatment, while atogepant is approved for preventive therapy. These oral options provide flexibility and are particularly beneficial for individuals who prefer not to use injectable medications.(15)

**Personalized Therapy**

Migraine pathophysiology has led to more personalized treatment strategies, considering individual patient profiles, comorbidities, and preferences. This approach aims to enhance treatment efficacy and patient satisfaction.These developments represent significant progress in chronic migraine management, offering new avenues for relief, particularly for women who are disproportionately affected by this condition [16]

# Botulinum Toxin Injections

* Botulinum toxin type A, the FDA-approved drug for the administration of chronic migraines.
* It is believed that Botox inhibits the release of neurotransmitters causing pain and blocks the activation of the trigeminal nerve in migraine pathogenesis.
* The injections are given at various points in the head and neck every 12 weeks. Chronic migraines have been decreased in frequency and severity with Botox injections.
* For chronic migraines, patients who are non-responsive to other preventive treatments can be improved by Botox. [17]



**Fig 5: Botulinum toxin injection**

## **NON-PHARMACOLOGIC THERAPY**

**Neuromodulation Devices**

* Cefaly Device: A wearable device that provides transcutaneous electrical nerve stimulation (TENS) to the forehead to reduce migraine frequency.
* sTMS: Single-pulse transcranial magnetic stimulation is a non-invasive device that targets the brain’s cortex to reduce migraines.
* Transcranial Direct Current Stimulation (tDCS): This technique uses a low electrical current to modulate brain activity and reduce the frequency of migraines.
* The sphenopalatine ganglion (SPG) stimulation system is a non-invasive neuromodulation device for migraine relief.
* The SPG system targets the sphenopalatine ganglion, a nerve cluster that is involved in the transmission of pain during a migraine [18].
* Patients can use a small device placed in the mouth to deliver electrical stimulation to this nerve, effectively reducing the frequency and severity of migraines.
* These devices are designed for home use and offer a promising option for patients seeking to manage migraines without systemic medications [18][19].



### Fig6: Neuromodulation Device

**Cognitive Behavioral Therapy (CBT)**

* Mechanism: Addresses the psychological and behavioral factors contributing to migraine. Advancements: Studies continue to show that CBT can reduce

Migraine frequency and intensity, especially in patients with stress-related or chronic migraine [20].

### Transcranial Magnetic Stimulation (TMS)

* Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulation treatment that employs magnetic pulses to stimulate the areas of the brain where the attacks of migraine are initiated.
* TMS has been approved by the FDA for acute treatment of migraine and has been used in decreasing the frequency of attacks and its symptoms.
* It is generally used on the forehead and gives the motor cortex magnetic pulses that would modulate cortical excitability in reducing susceptibility to migraines.
* In studies, it has been reported that TMS could provide notable relief from migraine attacks without many side effects. In this regard, it remains an attractive option for the patients who seek non-pharmacological treatment [21][22].

### Cefaly Device (Transcutaneous Electrical Nerve Stimulation)

* The Cefaly device is a headband-like device that uses TENS stimulation to the trigeminal nerve, which is the primary nerve involved in migraine attacks.
* FDA approved for the prevention of migraines, the device sends electrical impulses to the forehead and has been shown to reduce the frequency and severity of migraines over time.
* The Cefaly device is a non-invasive, drug-free treatment for chronic migraines that can be used at home. It is best suited for patients who prefer not to use medication or have contraindications to drug therapy [23][24].

### Genetic Research and Personalized Medicine

* New genetic research opens the door to personalized migraine treatments for an individual based on their genetic profile.
* Some studies have identified several genes that have an increased risk of developing migraines. These include genes associated with serotonin regulation, ion channels, and vascular function [25].
* Personalized medicine focuses on the matching of the most effective treatment with patients based on their unique genetic makeup, thereby allowing for more precise and efficient care.
* Biomarkers (biological indicators) research is also opening doors to more accurate treatment outcome predictions, which can help tailor therapy selection for the individual patient [25][26].

### New Preventive Medications

* Beta-blockers, antiepileptics, and antidepressants have been used for ages in the prevention of migraines; however, new forms and formulations are being developed with better efficacy and fewer adverse effects.
* Lasmiditan, a ditan (serotonin 5-HT1F receptor agonist) is also being studied in the prevention of patients of chronic migraine [27].
* New formulations of already existing medications, such as topiramate and valproic acid, are being adjusted to make them more efficacious and less harmful thereby making the whole experience of suffering from these migraines much better for the patients.
* CGRP antagonists have also been studied for their possible use in prevention, adding to their current use only in acute treatment [28].

### Advances in Diagnostics and Monitoring of Migraines

* The progress with diagnostic tools, such as the improved MRI and fMRI, have gradually enhanced our knowledge regarding brain involvement in migraine disease diagnosis.
* Mobile applications as well as wearable technologies continue to be developed and launched to monitor the frequency of migraines, triggers and how severe they are. It increases the management of more treatment options and a very more personalized approach.
* The continuous biomarker research is also assisting in identifying objective measures of migraine for faster diagnosis and effective treatment planning [29].
* Modern imaging tools help to understand the Pathophysiology and detect structural or functional abnormalities associated with migraine [30].

**Conclusion**

The evolving landscape of migraine therapy highlights a paradigm shift toward more targeted, effective, and patient-centric approaches. Key breakthroughs—such as CGRP inhibitors, gepants, ditans, neuromodulation devices, and botulinum toxin—are expanding the therapeutic arsenal beyond conventional treatments, offering significant relief with improved safety profiles. Non-pharmacological innovations and personalized treatment strategies further emphasize the importance of tailoring interventions to individual patient needs. These developments not only enhance clinical outcomes but also empower patients with more choices and better quality of life. Continued research, integration of genetic insights, and multidisciplinary collaboration will be pivotal in shaping the future of migraine management.

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