**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%:

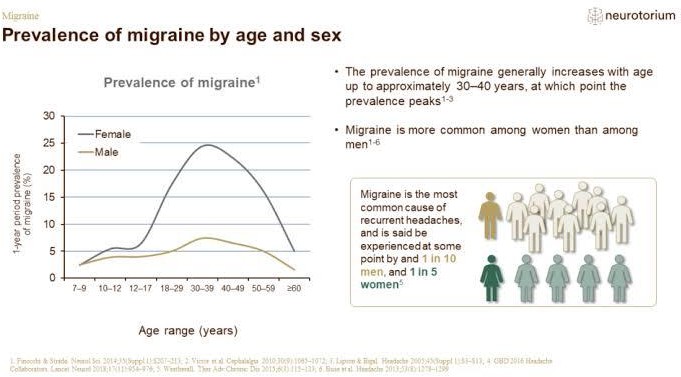
Global: The 1-year prevalence of migraine is estimated at 15% worldwide. US: A 2018 survey found that 15.3% of adults in the US experience migraine or severe headache. Women vs men: Migraine is about three times more common in women than in men. The World Health Organization (WHO) recognizes headache disorders, including migraine, as a significant global health burden, emphasizing their impact on individuals and societies. Migraine is a common neurological disorder associated with substantial disability and reduced quality of life, affecting millions worldwide.

Key points about migraine from WHO's perspective:

* **High Prevalence:** Migraine is one of the most common neurological disorders, affecting around 12% of adults in Western countries.
* **Disability and Reduced Quality of Life:** Migraine is a leading cause of temporary disability and significantly impacts individuals' quality of life due to pain, disability, and financial costs.
* **Comorbidities:** Migraine is associated with various other conditions, including depression, cardiovascular disease, sleep disorders, and psychiatric disorders.
* **Underestimation of Burden:** Many individuals with migraine are not appropriately diagnosed or treated, leading to an underestimation of the overall burden.
* **Global Burden:** Migraine contributes significantly to the global burden of neurological disorders, measured by Disability-Adjusted Life Years (DALYs).
* **Temporal Trends:** The global burden of migraine has increased from 1990 to 2021, with female individuals bearing a greater burden but male individuals showing a faster growth rate.
* **Need for Targeted Strategies:** Disparities across regions, countries, age groups, and sexes highlight the need for targeted public health strategies to mitigate the impact of migraines.
* **Under-diagnosis and Under-treatment:** Despite the availability of effective treatments, migraine is often underdiagnosed and undertreated, potentially due to factors like lack of awareness and access to care.

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].

**PATHOGENESIS PATHWAYS**

**Trigeminal System Activation**: The trigeminal nerve, which carries pain signals from the head and face, is central to migraine.

* During a migraine, the trigeminal nerve and its associated blood vessels are activated, leading to pain signals being sent to the brain.
* Neuropeptides, like calcitonin gene-related peptide (CGRP), are released from the trigeminal nerve, contributing to pain and inflammation.

**Cortical Spreading Depression (CSD)**: In migraine with aura, a phenomenon called cortical spreading depression (CSD) occurs.

* CSD is a wave of intense electrical activity that spreads across the brain cortex, potentially disrupting neuronal function and triggering aura symptoms.
* CSD may also contribute to the headache phase by sensitizing the trigeminal system.

**Neurogenic Inflammation**: Activation of the trigeminal system leads to the release of inflammatory substances, including CGRP and other neuropeptides.

* These substances cause vasodilation (widening of blood vessels) and increased permeability of blood vessels in the meninges (membranes surrounding the brain and spinal cord).
* This process, known as neurogenic inflammation, contributes to the pain and other symptoms of migraine.

**Central Sensitization**: The trigeminal system can become sensitized, meaning that the pain pathways become more reactive to stimuli.

* This sensitization can lead to heightened pain perception and make the individual more susceptible to future migraine attacks.

**Genetic and Environmental Factors**: Migraine has a strong genetic component, with various genes being implicated in susceptibility.

* Environmental factors, such as stress, sleep disturbances, and certain foods, can trigger migraine attacks in predisposed individuals.

**Premonitory and Postdrome Phases**: Migraines can have premonitory symptoms (e.g., mood changes, fatigue) that occur hours or days before the headache.

* The postdrome phase follows the headache, with symptoms like fatigue, cognitive difficulties, and mood changes.[5]

### 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 [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].

**Preventative Treatment Options:**

* **Beta-blockers:**

Propranolol and metoprolol are commonly prescribed and can cause hypotension, bradycardia, and fatigue.

* **Antidepressants:**

Amitriptyline and venlafaxine are used, particularly for patients with depression or anxiety, and can cause QT prolongation, nausea, and dizziness.

* **Anticonvulsants:**

Valproic acid and topiramate are used and can cause nausea, paresthesia, and difficulty concentrating.

* **CGRP Monoclonal Antibodies:**

Erenumab, fremanezumab, galcanezumab, and eptinezumab are injectable medications that target the CGRP pathway. Injection site reactions are the most common side effect.

* **Neuromodulation Devices:**

Non-invasive devices like vagus nerve stimulators can be used for prevention, especially for those who don't tolerate or respond to medications.

* **Botulinum Toxin:**

OnabotulinumtoxinA is injected to prevent chronic migraines, particularly those with 15 or more headache days per month [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].

**Physical Damages from Device Overuse**

* **Musculoskeletal Problems:** Prolonged use of devices can lead to neck pain, back pain, and carpal tunnel syndrome due to poor posture and repetitive motions.
* **Eye Strain:** Staring at screens for extended periods can cause eye strain, blurred vision, and headaches.
* **Repetitive Strain Injuries:** Activities like typing and using a mouse can lead to repetitive strain injuries in the hands and wrists.

**Mental Health Damages from Device Overuse**

* **Anxiety and Depression:** Excessive device use has been linked to increased anxiety and depression, potentially due to social comparison and exposure to negative online content.
* **Sleep Disturbances:** The blue light emitted from screens can interfere with sleep patterns, leading to insomnia and fatigue.
* **Social Isolation:** Excessive device use can reduce face-to-face interactions, potentially leading to social isolation and loneliness [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].
* Monoclonal antibodies that target calcitonin gene-related peptides may prevent migraines; however, their accessibility and safety are problems. Antiepileptics, beta-blockers, and neuromodulation devices are also available. Wearable technology offers customized monitoring and intervention [31].
* Moreover, recent studies have provided new findings in the genetic causes, anatomical and functional characteristics, and pathological potentials of migraine. For example, genomic loci associated with migraine were enriched in genes that are expressed in gastrointestinal tissues [32]
* That the diagnosis of headache disorders is primarily based on patient history provides a valuable opportunity for developing and evaluating digital tools to diagnose and manage headache types. Headache disorders remain largely underdiagnosed and misdiagnosed, and thus are undertreated and mistreated.Delays in accurate diagnosis lasting more than a decade lead to a higher risk for chronicification and increased complexity in headache treatment. Digital tools have the potential to close the gap between accurate diagnosis and increasing headache burden. Daily monitoring of headache incidence and related attributes using e-diary reduces diagnostic errors due to recall bias. Automated prediction of headache attacks and medication overuse can be made by using data-driven machine learning approaches [33]

Available abortive medications have efficacy rates as high as 80%, but only a minority of afflicted patients currently receive these therapies. While reducing headache pain, they also restore function, enabling an individual to return to work, family, and personal commitments. Future progress in migraine management resides in early identification and optimization of migraine treatment. This article focuses on diagnosis and treatment [34]

**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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**Reference:**

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