International Journal of Community Medicine and Public Health
Manorenj S. Int J Community Med Public Health. 2025 Apr;12(4):1952-1964
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20250952

Review Article

Acute migraine: an overview

Sandhya Manorenj*

Department of Neurology, Princess Esra Hospital, Deccan College of Medical Sciences, Hyderabad, Telangana, India

Received: 21 January 2025
Revised: 17 March 2025
Accepted: 19 March 2025

***Correspondence:**
Dr. Sandhya Manorenj,
E-mail: drsandhyamanorenj@gmail.com

ABSTRACT

Migraine is a primary headache disorder that affects people of all ages. It is the second most common type of headache disorder after tension headache. Migraine headache usually begins in adolescence, peak in the third decade of life, and becomes less frequent and less severe in later decades. Migraine affects women three times more often than men. Migraine can be very debilitating and can significantly impair an individual's ability to perform daily activities. Creating a clinical review on acute migraine and its management, using a pragmatic approach based on recent advances. The author reviewed the available literature on migraine and identified relevant articles through a literature search in the PubMed database to create this review. Migraine diagnosis is based on clinical examination and medical history, and imaging is usually not required. There are two main types of pharmacological treatment for migraine: abortive treatment to stop acute attacks and prophylactic treatment or preventive medication to reduce the frequency and severity of attacks. The treatment of migraine is constantly improving with new target-specific treatments, neuromodulation devices, and non-oral formulations of established medicines. This comprehensive review focuses on recent guidelines, newer approved drugs, and emerging therapies for managing acute migraine.

Keywords: Migraine, Primary headache disorder, Treatment of acute attack

INTRODUCTION

Migraine is the second most common cause of primary headaches worldwide, causing moderate to severe headaches, and is often accompanied by symptoms such as nausea, vomiting, sensitivity to light and sound, and fatigue.[1] Diagnosis is typically based on medical history and clinical examination. Migraine affects about 15% of the general population, with a higher prevalence in women.[1,2]

The treatment of migraine has advanced with the introduction of new medications with innovative mechanisms of action and the use of advanced drug delivery technology. The American Headache Society's 2019 guidelines recommend newer migraine medications for treatment.[3]

This review focuses on the currently available treatments for acute migraine, its basics, and its underlying causes.

METHODS

A targeted search was conducted on the PubMed database to find original research, review articles, and recent clinical practice guidelines published till April 2024. The search terms were “definitions migraine”, “prevalence migraine”, “pathophysiology migraine”, “genetics migraine”, "migraine acute treatment", "migraine neuromodulation devices”, “botulinum toxin”, “nerve blocks, childhood migraine”, “migraine with aura”, “migraine without aura”, “menstrual migraine”, “vestibular migraine”, “migraine in pregnancy”, “emerging therapies migraine” and FDA approved migraine drugs. This review is based on several ground breaking guidelines for the treatment of migraines that have been published.[3-11]

BASICS OF MIGRAINE

Prevalence of migraine

The global prevalence of migraine is around 14-15%, and it accounts for 4.9% of the global population's ill health measured in years lived with disability (YLDs).[12]

Women are more affected by migraine (16%) than men (4%), and chronic migraine accounts for 2% of the global population.[13]

Migraine can occur at any age, from childhood to old age. However, the incidence of active symptomatic migraine is highest around the age of 40 years and then decreases with age in both men and women.[14]

Definitions and key terminology

Migraine

Migraine is a familial, headache disorder with complex sensory processing disturbance.[13] Untreated migraine headache lasts for 4 to 72 hours. Most of the terms are given by International classification of headache disorder (ICHD-3).[15]

Migraine without aura

Also called common migraine or hemicrania simplex. Here headache is not preceded by aura.[15]

Aura

Aura are recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms [ICHD-3].[15]

Migraine with aura

Also known as classical migraine and is associated with migraine headache preceded with aura [ICHD-3].[15]

Episodic migraine

Episodic migraine refers to a headache occurring on less than 15 days a month. Low-frequency episodic headache (LFEH) is when there are 0-8 headache days per month, while high-frequency episodic headache (HFEH) is when there are 10-14 headache days per month.[16]

Chronic migraine

Headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache [ICHD-3].[15]

Crystal clear days

These are the number of days in a month when a patient has no headaches and is completely free from headaches. Subtracting the number of crystal clear days in a month helps to determine the actual number of headache days.[17]

Preventive migraine drug

A drug is considered successful if it reduces migraine attack frequency or days by at least 50% within 3 months.[17]

Menstrual migraine

Also called catamenial migraine is of two subtypes; pure menstrual migraine and menstrually related migraine.

Pure menstrual migraine is defined as a migraine occurring entirely on day 1±2 of menstruation in at least two out of three menstrual cycles and at no other time in the cycle.

Menstrual-related migraine is defined as the same but may occur at other times in the menstrual cycle, not just around menstruation.[18]

Status migrainous

Persistent debilitating migraine attack (with or without aura) lasting for more than 72 hours with little remission, leading to functional disability.[19]

Stratified care

Patients with migraine may need more than one available option to treat their attacks, which is termed stratified care.[10]

Refractory migraine

Individuals having ≥8 monthly days of debilitating migraine headaches for at least 6 months with contraindication or failure of all preventive classes of drugs.[20]

Resistant migraine

Individuals having ≥8 monthly days of debilitating migraine headaches for at least 3 months with contraindication or failure of all preventive classes of drugs.[20]

Treatment failure

It is declared after an adequate attempt (i.e., adequate dose and duration: 2 months for oral preventatives, 3 months for monoclonal antibodies targeting the calcitonin gene-related peptide, 6 months for on a botulinum toxin A).[20]

Debilitating attack

An attack is debilitating when it causes serious impairment to daily activities in spite of the use of an adequate dose of symptomatic medication.[20]

Rescue therapy

This is intensive therapy given in, emergency department, or inpatient setting to patients who do not respond to first-line treatment at least some of the time, and their migraine attacks do not respond to home treatments. Rescue therapy is usually a non-oral treatment like injectable, nasal sprays, and suppositories.[21]

Target goal in treatment of acute attack

Provide rapid and consistent freedom from pain and associated migraine symptoms without recurrence.[5]

Target goal in preventive treatment

Reduce the attack frequency, severity, and duration as well as the accompanying disability.[5]

Grading of migraine headache

Grading is based on migraine disability assessment questionnaire (MIDAS), which contains a 5-item questionnaire.[22] The patient needs to score the reduction in the performance, in days, of work/school, household work, and family/social activities. The score ranges from 0–270 and it indicates the overall level of disability due to headaches.[22, 23] There are four grades of disability based on MIDAS (Table 1).

Table 1: Grading of migraine.[30-32]

Grades of disability	Disability score based on MIDAS
Grade I, little or no disability	Score of 0–5
Grade II, mild disability	Score of 6–10
Grade III, moderate disability	Score of 11–20
Grade IV, severe disability (chronic migraine)	Score of ≥21
IV A	Score of 21–40
IV B	Score of ≥41

MIDAS: Migraine disability assessment questionnaire

PHASES OF MIGRAINE

There are four phases of migraine.[24]

Premonitory phase or prodromal phase

During this phase, symptoms such as yawning, mood changes, reduced concentration, sore neck, fatigue, malaise, food craving, increased frequency of urination, and thirst can occur for hours or days before the onset of a headache. During this phase, there is no headache.

Aura

Migraine with aura occurs in about one-third of migraine patients. It is described by temporary focal neurological symptoms that occur before or during some headaches and can last between 5 to 60 minutes. The most frequent type of aura is visual aura (90%) followed by sensory aura (30-54%) and language aura (31%). Motor, brainstem, and retinal aura are less common and usually atypical.

Headache

This phase is characterized by the throbbing headache of migraine due to the activation of the trigeminal system pathways. Headaches can be moderate to severe in intensity and disrupt activities of daily living. Headaches are usually long-lasting (more than 4 hours) and get worse with movements of the head. This phase is associated with other than headache symptoms like nausea, vomiting, allodynia, photophobia, osmophobia, and phonophobia.

Postdrome

This phase occurs following the resolution of the headache and is popularly known as the migraine hangover. Tiredness, drowsiness, inability to concentrate, and oversensitive to noise are the most common symptoms observed in this phase. Postdrome phase lasts for 24 to 48 hours. Prolonged and severe headache causes severe and prolonged postdrome phases and vice versa.

DIAGNOSTIC CRITERIA FOR MIGRAINE

Migraine is broadly classified into episodic migraine and chronic migraine based on the frequency of headache. Further, it is subdivided into migraine with or without aura depending on the presence of aura. ICHD-3 has given diagnostic criteria for various types of migraine.[15,25]

Diagnostic criteria of migraine without aura

A. At least five attacks fulfilling criteria B-D – B. headache attacks lasting 4-72 hour (untreated or unsuccessfully treated), C. headache has at least two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by or causing avoidance of routine physical activity, D. during headache at least one of the following: nausea and/or vomiting, photophobia and phonophobia, E. not better accounted for by another ICHD-3 diagnosis.[15]

Diagnostic criteria of migraine with aura

A. At least two attacks fulfilling criteria B and C – B. one or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, and retinal, C. at least three of the following six

characteristics: at least one aura symptom spreads gradually over ≥5 minutes, two or more aura symptoms occur in succession, each individual aura symptom lasts 5-60 minutes, at least one aura symptom is unilateral, at least one aura symptom is positive, and the aura is accompanied, or followed within 60 minutes, by headache, and D. not better accounted for by another ICHD-3 diagnosis.[15]

Diagnostic criteria of chronic migraine

A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C, B. occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura, C. on ≥8 days/month for >3 months, fulfilling any of the following: criteria C and D for 1.1 migraine without aura, criteria B and C for 1.2 migraine with aura, and believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative, and D. not better accounted for by another ICHD-3 diagnosis.[15]

Diagnostic criteria of vestibular migraine

A. At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 hours, B. current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD-3), C. one or more migraine features with at least 50% of the vestibular episodes: headache with at least two of the following characteristics: one sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity, photophobia and phonophobia, and visual aura, and D. not better accounted for by another vestibular or ICHD diagnosis.[15,25]

PATHOPHYSIOLOGY OF MIGRAINE

Current evidence shows that migraine is a complex cyclical brain disorder that occurs from abnormal sensory processing and dysregulation of homeostatic mechanisms. The association of multiple symptoms in migraine highlights the complex pathophysiology involving the entire nervous system involving somatosensory, autonomic, endocrine, and arousal networks.[13]

Migraine is an inherited disorder and multiple mechanisms are involved in the pathophysiology of migraine.[26] In the prodromal phase, there is activation of the hypothalamus and altered connectivity with the brain stem and brain region occurs leading to the various symptoms of the prodromal phase. Photophobia occurs due to the activation of the visual cortex while activation of the rostral dorsal medulla and periaqueductal gray matter is associated with nausea. Discomfort and neck stiffness cause activation of the trigeminocervical complex (brainstem and upper cervical spinal cord) where pain signals from trigeminal and cervical nerves converge. Aura occurs due to cortical spreading depolarization. This is a bioelectrical phenomenon where a wave of intense cortical neuronal activity spreads from one region to another. The wave is associated with hyperemia where there is intense cortical activity followed by cortical oligemia, which corresponds to the prolonged period of neuronal activity suppression.

Migraine headache is attributed to the activation of the trigeminovascular system. Both abnormal central sensory processing systems and activation of peripheral trigeminal nerve nociceptors are believed to mediate headache and implicate cortical spreading depression in head pain. The postdrome phase that occurs after the resolution of the headache has been associated with cerebral oligemia that occurs following hyperemia of cortical spreading neuronal activity. Hence there is a global reduction in cerebral blood flow which is mediated by brainstem nuclei leading to widespread vasoconstriction. This phase lasts for one to two days. Neuropeptides like calcitonin gene-related peptides (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), and serotonin play a role in the pathophysiology of migraine. Hence migraine headaches are also called neurovascular headaches based on their pathophysiology (Figure 1).

GENETICS OF MIGRAINE

Migraine is attributable to the complex interaction of genetic and environmental factors. There are more than 180 genetic variants responsible for causing migraine. Around 42% of migraine are inherited.[26]

Monogenic inherited migraines, including familial hemiplegic migraine (FHM) and migraine with aura associated with hereditary small-vessel disorders. FHM is inherited as an autosomal dominant inheritance. Here the identified genes code for proteins that are denoted in neurons, glial cells, or vessels, that ultimately increase susceptibility to cortical spreading depression. FHM has high penetrance; 70–90% of individuals with a pathogenic mutation clinically manifest the disease. FHM is subdivided into four types FHM1, FHM2, FHM3, and FHM4 based on the presence of mutations in the CACNA1A, ATP1A2, SCN1A, and PRRT2 genes respectively.

Polygenic inherited migraines have multiple variants and have a small effect size, while monogenic inherited models have genetic heterogeneity with clinical variability. Genetic variation in the TRPM8 gene, the TRPV1 gene, and HLA class I alleles have been associated with chronic migraine. Sporadic hemiplegic migraine (SHM) is an entity with hemiplegic migraine that occurs without any family history of hemiplegic migraine. This accounts for one-third of hemiplegic migraines. SHM occurs from a de novo mutation of one of the FHM genes with low penetrance and mosaicism, where the parents do not have any mutation. SHM is transformed to FHM when the mutation is transferred to subsequent offspring.

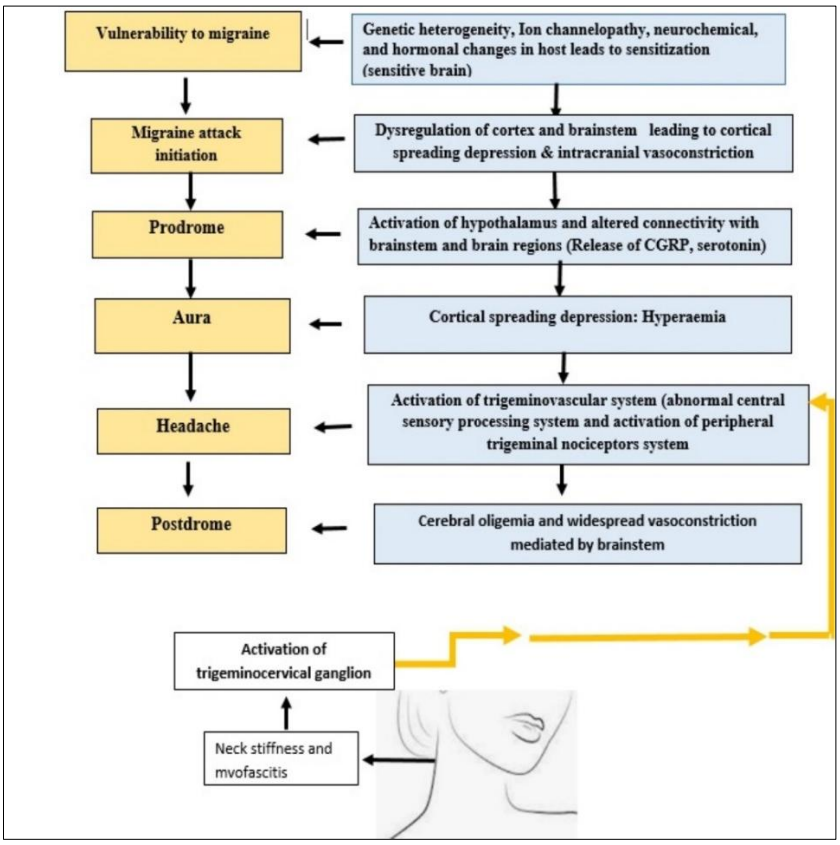

Figure 1: Pathophysiology of migraine.

MIGRAINE-LIKE HEADACHE

A variety of other neurological disorders can also present with symptoms similar to migraines. Migraine-like headaches can be seen in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); familial advanced sleep-phase syndrome (FASP), migraine and CSNK1D mutations; ROSAH (retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, migraine headache) syndrome, migraine and ALPK1 mutations; retinal vasculopathy with cerebral leukodystrophy (RVCL) caused by mutations in TREX1, and disorders due to COL4A1 and COL4A2 mutations are other small-vessel diseases that frequently involve migraines.[26-29]

TREATMENT OF ACUTE ATTACKS OF MIGRAINE

The acute treatments include behavioural management, nonspecific medications, migraine-specific medications, and neuromodulation. There are both pharmacological and non-pharmacological treatments for acute migraine.

Non-pharmacological treatment

To alleviate migraine symptoms, patients can rest in a quiet and dark area, hydrate themselves, and apply ice packs. Creams containing menthol, camphor, and lidocaine can also help. Other techniques include deep breathing, meditation, biofeedback, weight reduction education, lifestyle modifications, and neuromodulatory techniques. Combining pharmacological and non-pharmacological approaches is more effective.[30] Non-pharmacological migraine management offers many benefits, including reduced medication side effects, lower economic burden, decreased risk of medication overuse headaches, and safe use during pregnancy and lactation or when certain medications are not advisable.

Pharmacological treatment

It is broadly divided into two; non-specific treatment and migraine-specific treatment.

Non-specific treatments

There are three types of non-specific treatment for migraine: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and butalbital-containing products (Table 2).[4] Non-specific treatment is used for mild-moderate migraine attacks. Evidence suggests that opioids and butalbital-containing products cause more harm than benefit in people with migraines; thus, should not be prescribed for long periods or as a first-line treatment.[4] The FDA approved a new formulation of celecoxib in 2020 for acute migraine treatment. The recommended dose is 120 mg per day, available as a 25 mg/ml oral solution.[5]

Migraine-specific treatments

There are 5 categories of migraine-specific treatments for acute migraine headaches (Table 3).[4,5,7]

Triptans are considered the first-line treatment for moderate to severe migraine attacks.[4,10] There are seven FDA-approved triptans for acute migraine treatment. Triptans bind selectively to 5-HT1B and 5-HT1D serotonin receptors. Some triptans also activate 5HT1F receptors. Triptans are contraindicated in patients with vascular risks and cause serotonergic syndrome when co-prescribed with serotonergic drugs. Newer triptans like almotriptan, naratriptan, and frovatriptan have been shown to have fewer side effects and better tolerability than other triptans (Table 4).

Ergots have been used when triptans are ineffective.[4,10] It has poor tolerability because of nausea, vomiting, and cardiovascular effects. Dihydroergotamine (DHE) is a synthetic ergotamine with fewer side effects than previously used ergotamines. DHE is dosed intravenously, intramuscularly, subcutaneously, or nasally. DHE should be avoided in patients with peripheral vascular disease, cardiovascular disease, and uncontrolled hypertension.

Ditans are a novel category of drugs used for acute migraine treatments in patients who have vascular risks and triptans are contraindicated.[3] This is because they act as selective 5-HT1F receptor agonists. They act on the trigeminal system but do not cause vasoconstriction because of their low affinity for 5-HT1B receptors. Lasmiditan is the only drug available as a single dose per day for acute migraine attacks. Lasmiditan is available in tablet form as a single dose per day and comes in 50 mg, 100 mg, and 200 mg strengths. It is essential to note that taking a second dose of lasmiditan within 24 hours is not beneficial. However, it can be helpful for individuals who experience migraine onset later in the day or before sleep as it may induce a sedating effect for some patients. It is worth noting that lasmiditan may cause side effects such as dizziness, fatigue, paresthesia, and sedation. Therefore, patients should avoid driving for at least eight hours after taking the medicine.[5]

Gepants are calcitonin gene-related peptides (CGRP) receptor antagonists. CGRP plays an important role in the pathophysiology of migraine so migraine attacks can be prevented by blocking CGRP. Gepants block CGRP receptors located in the trigeminovascular system and thus do not cause vasoconstriction. Urbogepant, rimegepant and zavegepant are FDA-approved for the acute treatment of migraine in adults (Figure 2).[5,9,31-33]

Neuromodulation devices are non-pharmacological device used for the treatment of migraine. Currently, five non-invasive neuromodulation devices have been approved by the FDA, for the treatment of acute migraine attacks.[7,34-36] This includes external trigeminal nerve stimulation, single-pulse transcranial magnetic stimulation (Figure 3), non-invasive vagus nerve stimulation, remote electrical neuromodulation, and external concurrent occipital and trigeminal neurostimulation.[34-37] These devices are placed against the skin and are thought to modulate pain by electrical or magnetic impulses that translate to reduced activation of peripheral or central pain pathways. These non- pharmacologic options for the treatment of migraine help to alleviate potential side effects and interactions patients may experience with multiple oral medications. These devices are FDA-approved for the acute treatment and preventive treatment of migraine in adults and children above 12 years.[5,7,34-37]

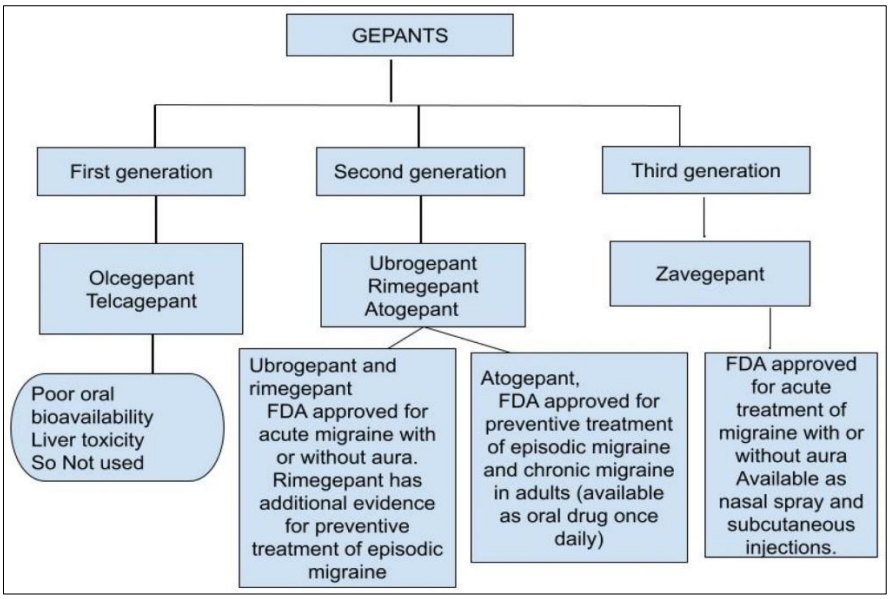

Figure 2: Classification of Gepants.

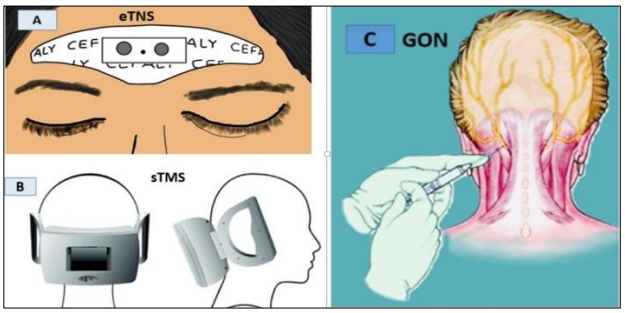

Figure 3: Neuromodulator devices and greater occipital nerve block.

External trigeminal nerve stimulation (e-TNS)

The CEFALY® device has FDA clearance for treating migraines using external trigeminal nerve stimulation (e-TNS), a non-invasive, drug-free approach. It stimulates specific nerve branches with a self-adhesive electrode pad placed on the forehead (Figure 4a). Once connected, the user can select one of two treatment programs: a daily 20-minute session to prevent migraine attacks and a 60-minute each of single or two sessions daily (total of 120 minutes/day) treatment for active migraine attacks. The maximum stimulation intensity of the current given by the device is 16 milliamperes. However, adverse effects have been reported such as paraesthesia in the distribution of stimulated branches of the trigeminal nerve.

Single-pulse transcranial magnetic stimulation (sTMS)

It is based on the principle of electromagnetic induction. A brief current pulse is sent through a coil within the device. When placed over a person's head for a short duration, it rapidly depolarizes neurons in a targeted area. To treat migraine symptoms, the device is switched on and positioned on the occiput (Figure 4b) by the patient, and the pulse is delivered with the pressing of a button. Three pulses up to 3 times per attack are required for acute treatment of migraine. Lightheaded, tingling, and tinnitus are the side effects observed in patients receiving sTMS.

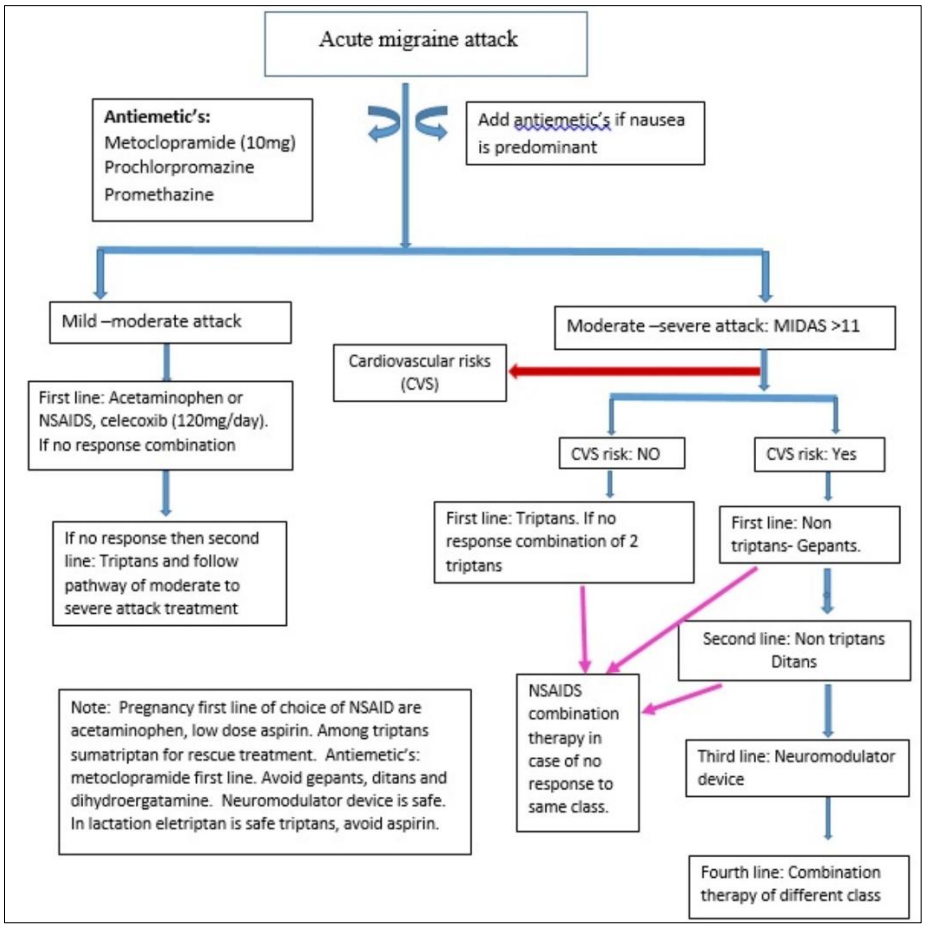

Figure 4: Algorithm for treatment of acute migraine attack.

Non-invasive vagus nerve stimulation (nVNS)

This non-invasive neuromodulation device is ideal for patients who have frequent migraine attacks who don't wish to take too many as-needed medications like abortive that can result in medication overuse headache. Here vagus nerve at the neck region (cervical vagus nerve) is stimulated bilaterally. Bilateral sides of the neck are stimulated for 120 seconds to the right and left of the neck within 20 minutes of the onset of attack. Repetition can be

done once after 20 minutes. The mechanism by which this device operates is that stimulation of the vagus nerve through skin inhibits the trigeminovascular pathway and suppresses the extracellular glutamate in the central nervous system that reduces the pain of migraine headaches. Nasopharyngitis and pain at the application site were frequent side effects.

Remote electrical neuromodulation

This is a device that stimulates the upper arm peripheral nerves to induce conditioned pain modulation. The device is applied to the upper arm for 45 minutes within 1 hour of the onset of migraine headache. Stimulation can be increased until perceptible but not painful. Side effects include transient warmth, redness, or tingling sensation in the arm.

External concurrent occipital and trigeminal neurostimulation (eCOT-NS)

This is the fifth neuromodulatory device approved by the FDA for acute treatment of migraine attacks in both episodic and chronic migraine. Patients with migraine with or without an aura external concurrent occipital and trigeminal nerve neuromodulatory device showed fast relief and freedom from migraine pain and the device was well tolerated. An ergonomic headset called the eCOT-NS is intended to externally stimulate the pericranial nerves in the head region. The headset contains two pairs of electrodes at the forehead that stimulate the bilateral trigeminal supraorbital and supratrochlear nerve branches while one pair of posterior electrodes stimulate the greater occipital nerve branch.

The device is adjustable to fit the scalp according to the anatomic variations so that the six electrodes are accurately arranged over the appropriate nerves to be stimulated each time the headset is worn. The stimulation is given for 30-60-minute duration within 30 minutes of the onset of the headache. The user can activate/deactivate the device and can adjust the stimulation intensity. Adverse effects of eCOT-NS are pain, unpleasant sensation during treatment, numbness or tingling at the local region.

Neuromodulation should be considered in patients who have poor tolerance for their current therapy, have found triptans to be ineffective, have contraindications to standard therapy, are overusing standard treatment, or prefer non-drug therapy.

Nerve blocks

Peripheral nerve blocks involve injecting local anesthetic or steroids in accessible nerve branches (greater occipital nerve, lesser occipital nerve, auriculotemporal nerve, supratrochlear nerve, and supraorbital nerve) on the head to treat headaches.[38] Greater occipital nerve blocks (Figure 4c) are an effective treatment for acute migraine. Injection can be repeated at 2-week or longer intervals as needed. Commonly used agents include lidocaine 1% to 2%, bupivacaine 0.5%, ropivacaine 0.5%, or a combination of these agents. Lidocaine or ropivacaine are safe in pregnant patients with migraine.[38,39]

Combination therapy

Combination treatments are effective when patients do not respond to one treatment alone. Combinations among the same class or different classes are often used. A combination with two or more analgesics is called combination analgesics indicated when treatment with one analgesic is not able to achieve target pain control after two hours of treatment. A combination of aspirin 500 mg, acetaminophen 500 mg, and caffeine 130 mg are established as effective for the treatment of acute migraine attacks.[4] Aspirin 500 mg to 1000 mg orally, ibuprofen 400 mg orally, and naproxen 500 mg to 550 mg orally also have level A efficacy; diclofenac 50 mg to 100 mg orally and celecoxib 25 mg/ml oral solution combination also have level A efficacy.[4] Combination of two triptans like oral triptan followed by parenteral sumatriptan after two hours of oral triptan. A combination of non-specific therapy and specific therapy like NSAIDS and triptans is another common practice. Common combinations include triptans or gepants with NSAIDS, an antiemetic, or both.

Management of acute migraine in special situations

It is shown in Table 5.[18,19,40-43]

Table 2: Showing non-specific treatment for acute migraine attacks.[4,5]

Variables	Acetaminophen	Non-steroidal anti-inflammatory drugs (NSAIDs)	Opioids and butalbital-containing products
Level of evidence (based on AHS 2015)[4]	Level A	Level A	Butorphanol nasal spray-level A, codeine-level B/C, tramadol-level B
Dose	1000 mg for non-incapacitating headache	Aspirin-900 mg, diclofenac-50 mg, 100 mg, and oral dissolvable powder, ibuprofen-200 mg, 400 mg, naproxen-500 mg, 550 mg	Butorphanol 10 mg/ml nasal spray (note: evidence showed that this group of drugs have more side effects than benefits, hence to be avoided as first-line treatment for acute migraine)

Continued.

Variables	Acetaminophen	Non-steroidal anti-inflammatory drugs (NSAIDs)	Opioids and butalbital-containing products
Side effects	Nausea, vomiting, headache, and insomnia. Hepatotoxicity at higher frequent dosing.	Gastrointestinal ulcers and bleeding, increased risk of cardiovascular events like myocardial infarction, medication overuse headache, renal failure, stroke, liver failure, and oedema. Aspirin is one NSAID devoid of side effects like myocardial infarction and stroke.	Sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression

AHS: American headache society; level A evidence requires at least 2 class I studies; and level B evidence requires 1 class I or 2 class II studies, level A: strong evidence; level B: moderate evidence; level C: limited evidence

Table 3: Showing migraine-specific treatments for acute migraine (mnemonic TED GN).[4,5,7]

Drugs	Triptans (T)	Ergots (E)	Ditans (D)	Gepants (G)	Neuromodulation devices (N)
Level of evidence	Level A	Level A nasal route, level B for intravenous administration	Level A	Level A	Level A
Drugs available	7 drugs mnemonic FARNESZ: frovatriptan, almotriptan, rizatriptan, naratriptan, eletriptan, sumatriptan, zolmitriptan	DHE: dihydroergot-amine	1 drug: lasmiditan	4 drugs: ubrogepant, rimegepant, and zavegepant for acute migraine treatment while atogepant for preventive treatment of episodic migraine.	5 non-invasive neuromodulatory devices: external trigeminal nerve stimulation, single-pulse transcranial magnetic stimulation, non-invasive vagus nerve stimulation, remote electrical neuromodulation and a combination of external concurrent occipital and trigem-inal neurostimulation.
Mechan-ism of action	5HT 1B/1D receptor agonist Some have 5HT1F receptor agonist (1B, 1D, 1F) - all causes vasoconstriction	5-HT1B/1D/1F receptors agonist and binds to 5-HT1A and 5-HT2A receptors (agonist) and to adrenergic, cholinergic, and dopaminergic receptors.	Selective 5-HT1F receptor agonists. They act on the trigeminal system but do not cause vasoconstriction because of their low affinity for 5-HT1B receptors.	CGRP receptor antagonists. Does not cause vasoconstriction so safe in stable cardiovascular disease.	These devices are placed against the skin and they modulate pain by electrical or magnetic impulses that renders to reduce activation of peripheral or central pain pathways
Indica-tion	First-line treatment for moderate to severe migraine attacks	Indicated who does not respond to triptans, in patients who have longer attacks or attacks with allodynia.	Indicated when there is inadequate respo-nse to or cardiovas-cular contraindication to a triptan and when migraine onset occur later in the day or may choose to use lasmiditan before sleep as it may carry a sedating effect for a small portion of patients	Indicated when triptans are ineffective or contraindicated.	To be considered in patients who have poor tolerance to standard therapy, have found triptans to be ineffective, have contraindications to standard therapy, are overusing standard treatment, or prefer nondrug therapy.

Continued.

Drugs	Triptans (T)	Ergots (E)	Ditans (D)	Gepants (G)	Neuromodulation devices (N)
Routes of administ-ration	Oral, nasal, subcutaneous, oral disintegrating	Non-oral agent, available as nasal spray and intrave-nous injections	Oral route	Oral route, oral disintegrating tablets available. Zavegepant available as nasal spray and subcutaneous administration.	External application, non-pharmacological non invasive

Table 4: Availability and doses of various triptans.

Triptans	Dose	Availability	Half-life and special indication
Sumatriptan	Sumatriptan 3 mg, 6 mg subcutaneous injection and DFN-02 (sumatriptan 10 mg with a permeation enhancer) nasal spray, oral tablet 50-100 mg (maximum 200 mg), nasal powder sumatriptan 22 mg dose using one 11 mg capsule insufflated in each nostril with a breath-powered delivery device (maximum 44 mg in 24 hours)	Oral tablet, nasal spray, subcutaneous injection, nasal powder, combination tablet with naproxen	2-4 hours, preferred in pregnancy and lactation
Rizatriptan	5 mg	Oral tablet, orally disintegrating tablet	2-4 hours, only triptan approved by the FDA for children
Zolmitriptan	2.5 mg, 5 mg oral tablet, 5 mg nasal spray	Oral tablet, an orally disintegrating tablet, nasal spray.	2-4 hours, the nasal spray is preferred in migraine with vomiting.
Frovatriptan	2.5 mg	Oral tablet	Longer half-life: 6-26 hours, preferred in menstrual migraine, status migraine because of longer duration
Naratriptan	1 mg	Oral tablet	Longer half-life: 6-26 hours, preferred in menstrual migraine, status migraine because of longer duration. The only drug that acts in the premonitory phase.
Almotriptan	6 mg, 12.5 mg, 25 mg	Oral tablet	2-4 hours
Eletriptan	20 mg, 40 mg	Oral tablet	2-4 hours, preferred in breastfeeding.

Table 5: Acute treatment of migraine in specific circumstances.[18,19,40-43]

Special scenario	Acute attack treatment
Vestibular migraine[40]	Antiemetic's (dimenhydrinate), antivertigo medicine, analgesic (NSAIDS), triptans
Menstrual migraine[18]	NSAIDS (mefenamic acid, naproxen), long acting triptans (frovatriptan, naratriptan)
Pediatric migraine[41]	NSAIDS (ibuprofen and acetaminophen) in children and adolescents, triptans in adolescents
Status migrainosus[19]	Parenteral medication is preferred given the severity, injection metoclopramide, NSAIDS, Subcutaneous sumatriptan, combination, treatment with parenteral magnesium sulfate, dihydroergatamine, antiepileptics, corticosteroids, and anaesthetic agents
Pregnancy and migraine[42]	First line: non-pharmacological methods (behavioural intervention and lifestyle modifications); followed by NSAIDS: paracetamol, ibuprofen and acetaminophen are safe, aspirin dose of less than 100 mg is preferred; metoclopramide is used for

Continued.

Special scenario	Acute attack treatment
	hyperemesis safe for acute attack. Triptans: sumatriptan if paracetamol is inefficient. Behavior strategies, and nerve blocks. Neuromodulation and neurostimulation devices.
Lactating mother and migraine attack[42]	NSAIDS (paracetamol, acetaminophen, ibuprofen naproxen) and triptans (sumatriptan and eletriptan), neuromodulation and neurostimulation devices
Hemiplegic migraine[43]	NSAIDs and antiemetic's, similar to treatment of migraine with aura but avoid triptans as risk of increased ischemia is there. Intranasal ketamine given at the onset of attack has shown benefit in patients with familial hemiplegic migraine. Verapamil can be used as an abortive agent too. Neuromodulation devices
Migraine with aura	NSAIDS, antiemetic's and triptans (avoid triptans in hemiplegic migraine)

DISCUSSION

Therapy for migraine involves multiple classes of drugs with different mechanisms of action and pharmacokinetics. Among the non-specific treatments celecoxib is a newer add-on approved for acute attack. Specific treatments such as gepants and ditans are safer for patients with cardiovascular risks as they do not have vasoconstrictive potential. Zavegepant is the only drug available in non-oral form thus making it as drug of choice in acute attacks with severe emesis. Gepants do not cause medication overuse headaches, making them safer in medication overuse headaches. Neuromodulation devices are safe for treating migraine attacks even during pregnancy and in children above 12 years. Recently, the FDA has approved an additional neuromodulation device (external combined occipital and trigeminal neurostimulation), resulting in a total of five devices approved for treating acute attack and preventive treatment of migraine. An algorithm for treating acute migraine attacks is depicted in Figure 4.[5]

Limitations, are the review does not cover the triggers of migraine, various subtypes, detailed descriptions of each type and comparisons between individual drugs.

CONCLUSION

The treatment of acute migraine attacks involves various pharmacological and non-pharmacological choices that can be customized to meet the specific therapeutic requirements of individual patient. Non-oral formulations and neuromodulatory devices have demonstrated strong evidence of being effective with fewer side effects.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Manorenj S. Acute migraine: an overview. Int J Community Med Public Health 2025;12:1952-64.