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A REVIEW OF MIGRAINE: FROM MECHANISMS TO MANAGEMENT STRATIGIES

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ABSTRACT

A pulsing headache that is limited to one side and occurs in episodes lasting four to forty-eight hours is the hallmark of migraine, an enigmatic and frequently misunderstood ailment. It might be hard for friends, family, and co-workers to comprehend how someone with a migraine can be OK one minute and then have a painful headache the next. It is a complicated neurological disorder that can affect the entire body and cause a variety of symptoms, sometimes even without a headache. There are two typical forms of migraines: common migraine, which does not have an aura, and classical migraine, which has an aura or warning. There are two types of pharmacological treatment for migraines: acute and preventative. Prophylactic treatment is necessary for frequent, severe, and protracted migraine attacks. We talked discussed novel therapeutic possibilities as a result of our increased understanding of the pathophysiology of migraines. Symptoms of migraine include a severe headache, constant, throbbing pain, difficulty doing daily tasks, etc. Primary care physicians are consulted by most migraineurs who seek medical assistance. As a result, generalists should be knowledgeable in migraine diagnosis, prevention, and therapy. Nonetheless, there are numerous strategies to manage the illness and decrease its effects, which will ultimately lessen the interruption to daily life.

KEYWORDS: Migraine, pulsating headache, classical migraine, Preventive therapy, Aura, Migraine Triggers, Patient.

1. INTRODUCTION

A fundamental understanding of the head's pain-sensitive structures and pain pathways is necessary for understanding the pathophysiology of migraine. Almost all tissue in the head, face, and neck is sensitive to pain. These consist of the dura, intracranial and extracranial arteries, veins, periosteum, skin, muscles, sinuses, eyes, ears, teeth, gums, cervical roots, and cranial nerves. It is crucial to remember that the ventricular lining, pia, and brain parenchyma are not sensitive to pain. Trigeminal nerves (V1, V2, V3) are primarily responsible for transmitting pain sensation from the face and front of the head. The majority of the pain-sensitive supratentorial intracranial contents are also innervated by the trigeminal nerve's ophthalmic division (V1). The posterior scalp and posterior/inferior intracranial structures are served by the cervical roots (C2–3).

There are at least three neurons involved in the transmission of nociception from the head. First-order neurons are bipolar afferents that originate from anterior pathways (face/anterior head) and posterior cervical networks (posterior/inferior intracranial) via the trigeminal ganglion and dorsal root ganglia, respectively. The bipolar neurons in the trigeminal route descend to the C2 level in the brainstem through the spinal trigeminal tract. There, they meet up with the bipolar neurons from the dorsal root ganglia, and they both form synapses on the second-order neuron in the dorsal horn.[1]

As a result, trigeminal and cervical convergence occurs. Both the spinothalamic and trigeminothalamic routes, which ultimately culminate in the thalamus—more precisely, the ventral postero-lateral nuclei—are examples of the second-order pathways, which are essentially identical and ascend in several tracts. for the trigeminal domains and the ventral postero-medial nuclei for the cervical tracts. Information is subsequently transmitted from the third-order cell to the parietal lobe's somatosensory cortex. It's interesting to note that the pain tracts lack a homunculus, a specialized map found in other nervous system tracts related to sensation and motor function. Consequently, head, facial, and neck pain is frequently poorly localized because the cervical and trigeminal systems' fibers are not organized clearly inside the tracts, sending conflicting signals. With a basic understanding of the structures, neurons, and pathways

involved in creating pain, it becomes clearer why headache is a common phenomenon.[2] Migraine specifically is a frequent complaint of patients seen in the primary care setting, emergency room, neurology office, and at anaesthesia and pain centers. Knowledge of headache and migraine classification is helpful to the health care professional in dealing with these patients.

It becomes more evident why headaches are a typical occurrence when one has a rudimentary understanding of the structures, neurons, and pathways involved in producing pain. In particular, migraine is a common complaints from patients visited in anaesthesia and pain centers, emergency rooms, neurology offices, and primary care settings. Health care providers can better treat these patients if they are aware of the classifications for headaches and migraines.

Figure1: Migraine.

1.1 Subtypes of Migraine

Migraines can be classified into the following subtypes according to the Headache Classification Committee of the International Headache Society.[3]

- A migraine without aura: This category includes repeated episodes of headaches that last four to seventy-two hours. In most cases, the pain is unilateral, pulsating, moderate to severe, triggered by movement, and associated to light (photophobia), sound sensitivity (phonophobia), and nausea.
- Migraine with aura: Recurrent, completely reversible attacks lasting minutes are characteristic of this subtype. Usually, one or more unilateral symptoms, such as visual, sensory, speech and language, motor, brainstem, or retinal problems, are present, followed by headache and other migraine symptoms.
- Chronic migraine: This is characterized as a headache that lasts for more than three months and happens at least fifteen times in a month, with migraine symptoms appearing at least eight times a month.
- Probable migraine: This is a symptomatic migraine attack that does not fit the criteria for another form of headache and does not have one of the characteristics needed to meet the requirements for one of the previously mentioned conditions.

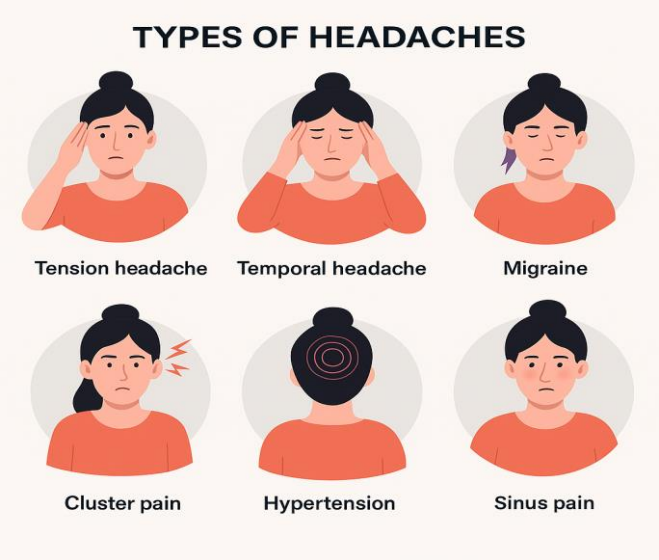

Figure 2: Types of Headaches.

1.2 Etiology

In order to diagnose and treat migraine headaches effectively, it is essential to comprehend their genesis. A confluence of neurological, environmental, and hereditary variables is thought to cause migraines. Studies reveal a connection between severe headaches and aberrant brain activity that impacts the brain's blood vessels, neurotransmitters, and nerve messages.[4]

1.2.1 Familial Hemiplegic Migraine

- Individual may be the first member of their family to suffer from a hemiplegic migraine, or it may happen infrequently. Type 3 is caused by mutations in the *SCN1A* gene (voltage-gated sodium channel type 1α-subunit).[7]
- One known cause is mutations in the proline-rich transmembrane 2 (PRRT2) gene.[9] A protein that interacts with the synaptosomal nerve-associated protein 25 (SNAP25) and may be involved in the control of voltage-gated calcium channels is encoded by the PRRT2 gene.[8]
- Familial types of migraine have also been linked to mutations in the SLC4A4 gene (solute carrier family 4 member 4).[9]

1.2.2 Genetics and Inheritance

There is a significant hereditary component of migraines; although no particular pattern of inheritance has been found, relatives of affected persons are three times more likely to get migraines than relatives of unaffected individuals.[10] [11] Multiple loci and genes with unclear functions in pathogenesis construct up the complicated genetic basis of migraine.

This is probably caused by many genetic sources at different genomic sites working together with environmental influences to determine a person's vulnerability and disease characteristics.[12] It may be possible to forecast specific preventative treatments by identifying these genes in people who suffer from migraine.

1.2.3 Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

Mutations in the NOTCH3 gene (notch receptor 3) on chromosome 19 cause CADASIL, an angiopathy with autosomal dominant inheritance. In about half of carriers, CADASIL can appear as migraine with aura (prodrome in 80%).[13]

1.2.4 Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy

HIHRATL is a novel hereditary autosomal dominant condition that affects retinal and cerebral vessels.

1.2.5 Hereditary endotheliopathy with retinopathy, nephropathy, and stroke

HERNS is a cerebroretinal vasculopathy linked to a locus on chromosome 3p21.

1.2.6 Migraine Triggers

Migraine headaches are caused by withdrawal or exposure to a number of factors.[14] 76% of patients in a retrospective analysis reported triggers.[15] While some elements may or may not be contributing factors, others are likely to be.

1.3 Epidemiology

Approximately 12% of people suffer from migraines, with yearly rates for women and men reaching up to 17% and 6% men respectively.[16] [17] [18] in children, girls are more likely than boys to have it.[19] Migraines are more common after adolescence, peak between the ages of 35 and 39, and then tend to decline as people age, especially after menopause.

With a stated risk of 40% if one parent has a history of migraine and 75% if both parents have a history of migraine and are affected, migraine continues to run in families.[16] With about 3% of all ER visits occurring each year, this ailment routinely ranks as the fourth or fifth most frequent cause of ER visits.[20] Furthermore, in terms of years spent disabled, migraine is regarded as the second leading cause of disability, following back pain.[19]

1.4 Pathophysiology

The pathophysiology of migraine headaches involves several elements of the central nervous system (CNS) and peripheral nervous system, however this is not entirely understood. Some of the most widely accepted ideas are explained in this section. Headaches were believed to be caused by vasodilation and auras by vasoconstriction, according to the earlier vascular theory of migraine; however, this idea is no longer accepted.[21]

Current theories suggest that multiple primary neuronal impairments lead to a series of intracranial and extracranial changes that cause migraines.[22]

Trigeminal afferents are activated by neuronal pannexin-1 mega channel opening, which is followed by caspase-1 activation. Following this, pro inflammatory mediators are released, nuclear factor kappa-B (NF-kB) is activated, and the inflammatory signal is transmitted to trigeminal nerve fibers around the pia mater vessels.[23]

Through both central and peripheral pathways, this process causes headaches by provoking inflammation in the pain-sensitive meninges and setting off a chain of cortical, meningeal, and brainstem events.[24, 25] The cerebral depression that creates the aura and the subsequent prolonged activation of trigeminal nociception that causes headaches can both be explained by this pathway.

According to theory, the aura is caused by the cortical spreading depression of Leão, which is a propagating wave of neuronal and glial depolarization that starts a cascade. It also activates trigeminal afferents and changes the permeability of the hematoencephalic barrier by activating brain matrix metalloproteinases.[26] It has been proposed that cortical spreading depression may happen in regions like the cerebellum, where depolarization is not consciously felt, in migraine without aura.[27]

The ophthalmic division of the trigeminal nerve innervates the anterior structures primarily which may explain why the anterior part of the head hurts. From neurons of the trigeminal nerve and ganglia in the trigeminal nucleus caudalis, fibers from the upper cervical roots converge. The distribution of pain from anterior to posterior may be explained by this convergence, as these fibers ascend to the sensory cortex and thalamus.[28]

According to vasodilation, edema, and plasma protein extravasation, nociceptors, especially those in the trigeminal system, are activated, causing neurogenic inflammation. The release of substance P, calcitonin gene-related peptide (CGRP), and neurokinin A—vasoactive neuropeptides released by stimulation of the trigeminal ganglion—is linked to this process.[29] Patients with persistent headaches have been found to have higher quantities of these neuropeptides in their spinal fluid.[30, 31] Sensitization, a process in which neurons become more sensitive to stimuli, can result from neurogenic inflammation. Clinical pain feelings and the change from episodic to chronic migraines may be explained by this.[32] Neuropeptides believed to play a role in migraine pathogenesis include the following.

1.4.1 Serotonin: Although the precise mechanisms are still up for question, serotonin is released from the brainstem serotonergic nuclei and is believed to play a role in migraine. Serotonin levels are likely to drop in between migraine attacks, which could lead to a malfunction in the serotonin pain inhibition pathway. This reduction can contribute to migraine symptoms by activating the trigeminal system. Cortical projections from brainstem serotonergic nuclei, central pain control pathways, or cranial arteries may all be affected directly by serotonin.[33]

1.4.2 Calcitonin gene-related peptide: Trigeminal ganglion neurons are rich in CGRP, which is also emitted from the central and peripheral nerve terminals. It is the trigeminal ganglion that secretes CGRP. When CGRP is released from peripheral terminals, it causes nitric oxide synthesis to rise, which in turn makes trigeminal nerves more sensitive.[34] In addition to mediating pain transmission from trigeminal vessels to the central nervous system, CGRP is a potent vasodilator of cerebral and dural vessels, which contributes to neurogenic inflammation.

1.4.3 Pituitary adenylate cyclase-activating polypeptide: Due to its high concentration during migraine episodes and the potential for infusion to cause migraines in sensitive patients, PACAP may also play a key role in mediating migraine attacks.

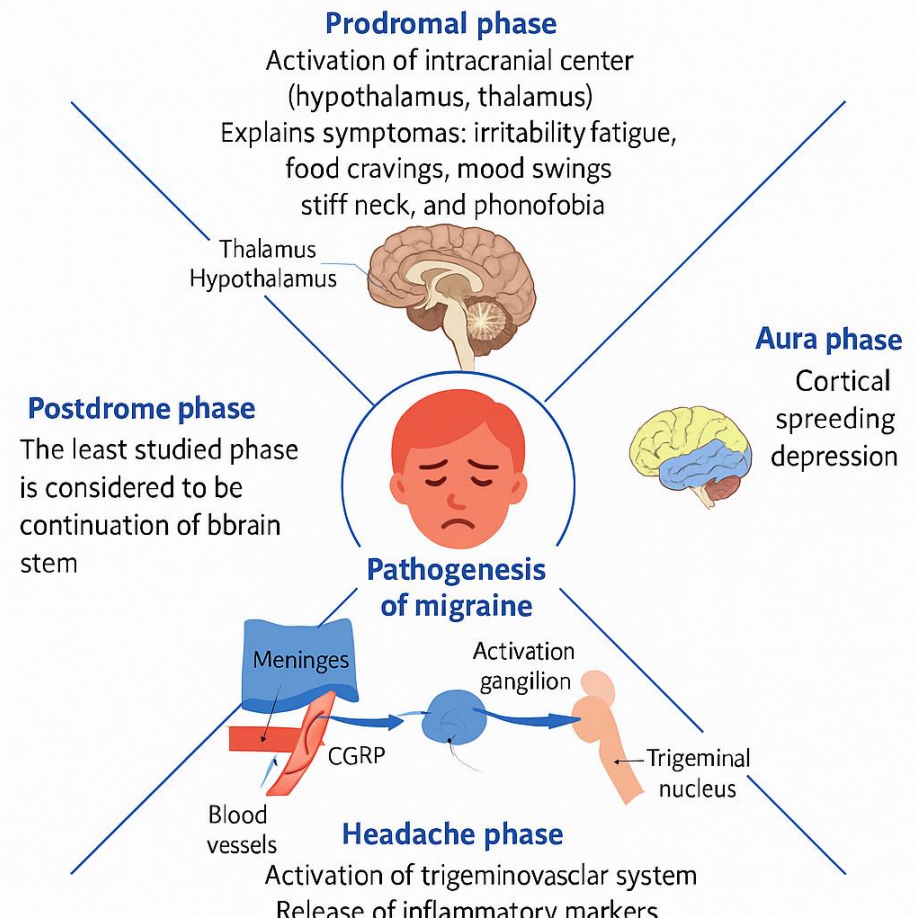

Figure 3: Pathophysiology of Migraine.

1.5 History and Physical

The course of a migraine episode is usually characterized by various phases, each with its own set of symptoms. For efficient management and patient education, it is essential to understand these phases.

The 4 phases identified in migraine attacks are as follows.

1.5.1 Prodrome: Premonitory symptoms associated with hypothalamic activation (dopamine).[35, 36]

- Prodromal symptoms might last for up to 24 to 48 hours before to the onset of headaches in about 77% of patients. Females are more likely than boys to go through this period (81% versus 64%).
- Yawning (34%), mood swings, lethargy, stiff neck, light and sound sensitivity, restlessness, trouble focusing, coldness, desires, sweating, increased energy, thirst, and edema are common complaints.

1.5.2 Aura: About 25% of cases involve changes in blood circulation, neurovascular integration, and cortical function.[37]

- Auras must be fully reversible by definition.

- Auras can precede the headache or present it simultaneously.
- The most common positive visual symptom is scintillating scotoma (an area of absent vision with a shimmering or glittering zigzag border).
- Visual auras are the most frequent.
- Language auras, which consist of transient dysphasia, are infrequent.
- Motor auras are rare and involve complete or partial hemiplegia of the limbs and face.
- Sensory auras are also common and can follow visual symptoms or occur independently.
- Tingling sensations, usually present on 1 side of the face or a limb, are considered paresthesias.

1.5.3 Headache: Additional changes in blood circulation and function of the brainstem, thalamus, hypothalamus, and cortex can occur.

- The headache usually has a pulsating or throbbing sensation, is unilateral, and gets worse in the first few hours.
- Allodynia, rhinorrhea, photophobia, phonophobia, lachrymation, osmophobia, nausea, and vomiting can all be correlated with the intensity.
- The headache can last from hours to days.
- Patients may seek relief in dark places, and the pain usually resolves with sleep.

1.5.4 Postdrome: Persistent blood changes with symptoms after headache termination.

- This phase consists of movement-vulnerable pain in the exact location of the previous headache.
- Common symptoms include exhaustion, dizziness, difficulty concentrating, and euphoria

2. Evaluation

Based on the patient's medical history, physical examination, and meeting diagnostic requirements, migraine is diagnosed. Note the patient's age, gender, race, and occupation, among other demographic characteristics. Answers to comparatively easy questions are among the additional information that has to be obtained from the patient.

Patients should also be asked regarding speech or thought abnormalities, as well as somatosensory disturbances such unilateral tingling or creeping numbness in the face and arm. A few aura signs that could point to rare migraine types are as follows.

- Motor weakness
- Dysarthria
- Hypacusis
- Diplopia
- Ataxia
- Vertigo
- Tinnitus
- Decreased level of consciousness

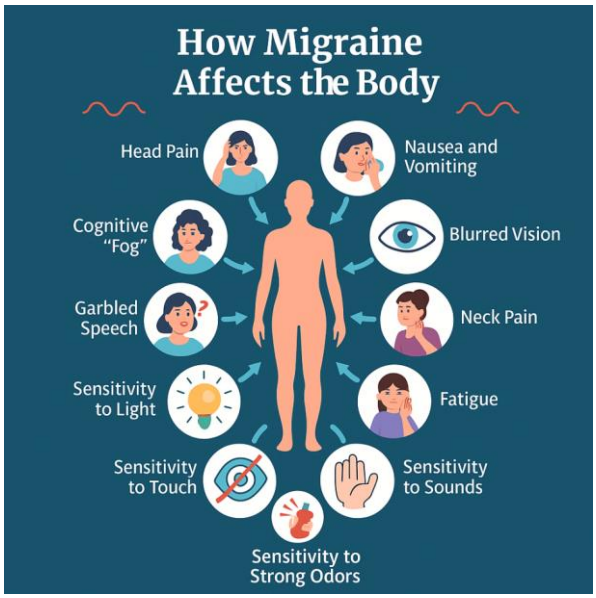

Figure 4: How Migraine Affects the Body.

2.1 Diagnosis of migraine: The International Headache Society developed the diagnostic criteria for migraines[38], which are summed up in Table1. The diagnostic standards for MO and MA are different. At least five headaches in four to seventy-two hours are a defining characteristic of MA. Additionally, MA exhibits pulsation, unilateral location, severe pain, or headache worsening during everyday activities. Phonophobia or photophobia, nausea, and vomiting accompany these symptoms.

Table 1: The diagnostic criteria for migraine headache as formulated by the International Headache Society.[38]

Without aura	With aura
• **Minimum of five headaches within 4–72 h.**	• Minimum of five headaches, among which at least two episodes must be accompanied by an aura.
• **Pulsation.**	• The headache should begin with, or be within 60 min of, the aura.
• **Unilateral location.**	• Reversible dysphasic speech.
• **Intense pain.**	• unilateral sensory.
• **Exacerbation of headache with routine activities**	• homonymous visual symptoms.
• **These features are accompanied by vomiting or nausea and phonophobia or photophobia.**	• Minimum of one symptom that gradually increases with time and each symptom ranges from 5 to 60 min.

Importantly, the headache and symptoms should not be ascribed to any other illness. A minimum of five headaches, with at least two of those episodes accompanied by an aura, are required for the diagnosis of migraine with the usual aura. The headache should start or happen within sixty minutes of the aura. Reversible dysphasic speech or unilateral sensory or homonymous visual symptoms must be included in the aura. At least one symptom, lasting between five and sixty minutes, must progressively worsen over time[38] The features should not be accounted for by a secondary disorder.

2.2 Investigations

To diagnose migraine, no particular tests are needed. The primary method of diagnosing migraine is history. To rule out other potential headache causes, imaging procedures and blood testing can be carried out. Magnetic resonance imaging (MRI) and computed tomography (CT) neuroimaging can be utilized for confirmation, even if a clinical examination can identify a variety of neurological disorders and illnesses.

2.3 CT Neuroimaging Studies

CT studies have been conducted on patients with migraine. These investigations have identified anomalies in a certain percentage of migraine cases. Two patients had gliomas, six had cerebral infarcts, and six had periventricular edema, according to a study that involved 94 people.[39], [40] In a different investigation, localized atrophy, generalized atrophy, and other abnormalities were observed in 25 out of 53 individuals.[41] Out of 453 migraine instances, one had a choroid plexus papilloma. Hospitalized cases have been shown to have low-density areas and ventricular hypertrophy. Some investigations have also noted the following: hydrocephalus, subdural hematoma, primary neoplasm, metastatic neoplasm, acute infarction, and subarachnoid hemorrhage. In older people, focal atrophy is very common. Ischemia, atrophy, calcifications in the basal ganglia, and ventricular enlargement are among the abnormalities that are commonly seen. Usually, the atrophy is a reflection of aging.[42]

2.4 MRI Neuroimaging Studies

White-matter lesions have been identified by MRI studies as being associated with the clinical characteristics and personal characteristics of migraine patients. White-matter anomalies are more common in patients with diabetes, hypertension, and cardiac disease. White matter foci are substantially more common in MA patients than in MO individuals. Heterotopy and atrophy of the frontoparietal and cortical regions are among the incidental findings. Intracerebral abnormalities are more common in headache patients than in non-headache patients. White-matter lesions are also seen in certain younger migraineurs. Additionally, some migraine sufferers have been shown to have meningiomas, petrous apex cholesterol cysts, and cortical abnormalities. WMHs and pituitary abnormalities have been seen in MRI investigations.[43]

2.5 Combined CT and MRI Studies

Patients with migraines usually have their neurological condition evaluated using both CT and MRI scans. No substantial abnormalities were found on CT scans, although Wang et al. found abnormalities on MRI scans in 4 out of 688 individuals. Among the abnormalities were hydrocephalus and malignancies of the throat and nose. Some patients with late-onset migraine, defined as those who get migraines after the age of 40, have cerebral infarction and carotid atheroma on their CT and MRI scans. However, neuroimaging is normal in 93% of the cases. Multiple foci were seen on T2 MRI but not on CT scans when 74 participants' MRI and CT scans were compared. In a different investigation, both CT and MRI neuroimaging revealed isolated or widespread ventricular enlargement in 26 participants.

3. Treatment / Management

3.1 Prophylaxis

Table 2: Migraine Prophylaxis Medications.

Medication	Dosage	Level of evidence
Divalproex/ sodium valproate	Divalproex/ sodium valproate	**A**
Metoprolol	50-200 mg/day PO	**A**
Propranolol	80-240 mg/day PO	**A**
Timolol 20-30 mg/day PO	20-30 mg/day PO	**A**
Topiramate	25-100 mg/day PO	**A**
Amitriptyline	10-150 mg/day PO	**B**
Nadolol	40-240 mg/day PO	**B**
Venlafaxine ER	37.5-150 mg/day PO	**B**
Atenolol	50-200 mg/day PO	**B**
Candesartan Carbamazepine Clonidine Cyproheptadine Guanfacine Lisinopril	Dosing varies	**C**

Nebivolol Pindolol		
Onabotulinum toxin A	Recommended total dose 155 units. Administer 5 units/0.1 mL per site at 31 total IM injection sites	**U**
Short-term prevention Associated with Mensturation		
Naratriptan Zolmitriptan	1 mg bid for 5 days perimenstrually 2.5 mg bid or tid perimenstrually	**B**

bid indicates twice daily; ER, extended release; IM, intramuscular;
PO, by mouth; tid, 3 times daily.
aLevel of evidence: A = established as effective, B = probably effective,
C = possibly effective, U = conflicting or inadequate evidence.

3.2 Treatment of Acute Migraine

Table 3: Acute Migraine Treatment.

Medication	Dosage	Level of evidence
Acetaminophen (APAP)**a** Almotriptan APAP/Aspirin (ASA)/caffeine**a** ASA**a** 500 mg PO Butorphanol**a** Diclofenac Dihydroergotamine (DHE) Eletriptan Ibuprofen Naproxen**a** Naratriptan**a** Rizatriptan**a** Sumatriptan Sumatriptan/naproxen Zolmitriptan	1000 mg PO 12.5 mg PO 500/500/130 mg PO 500 mg PO 1 mg nasal spray 50, 100 mg PO 2 mg nasal spray • 1 mg pulmonary inhaler 20, 40 mg PO 200, 400 mg PO 500, 550 mg PO 2.5 mg PO 5, 10 mg PO • 25, 50, 100 mg PO • 10, 20 mg nasal spray • 6.5-mg patch • 4, 6 mg SC 85/500 mg PO • 2.5, 5 mg nasal spray	A
Chlorpromazine IV**a** Codeine/APAP**a** DHE**a** Droperidol IV Ergotamine/caffeine**a** Flurbiprofen**a** Isometheptene**a**	12.5 mg IV 25/400 mg PO 1 mg IV, IM, SC 2.75 mg IV 1/100 mg PO 100 mg PO 65 mg PO 100 mg PO	B

Ketoprofen Ketorolac Metoclopramide IV**a** MgSO4 IV (migraine with aura) Prochlorperazine**a** Tramadol/APAP	30-60 mg IV/IM 10 mg IV 1-2 g IV 10 mg IV/IM • 25 mg PR 75/650 mg PO	

IM indicates intramuscular; IV, intravenous; MgSO4, magnesium sulphate; PO, by mouth; PR, per rectum; SC, subcutaneous.
a According to the 2000 American Academy of Neurology evidence review.
b Level of Evidence: A = Established as effective, B = Probably effective, C = Possibly effective.

Table 4: New and Currently Emerging Migraine Therapies.

Medication	FDA Approved	Formulation	Indication	Dosing	Common AE$_S$
Erenumab	Yes	Sc	Prevention	70 mg monthly, some may benefit from 140 mg monthly	Infusion reaction and constipation
Fremanezumab	Yes	Sc	prevention	225 mg monthly or 675 mg every 3 months	Infusion reaction
Galcanezumab	Yes	Sc	prevention	240 mg loading dose (2 consecutive injections of 120 mg); followed by monthly dose of 120 mg	Infusion reaction
Eptinezumab	No	Iv	prevention	No FDA-approved dosing	URI and UTI
Lasmiditan	No	Oral	acute	No FDA-approved dosing	Dizziness, somnolence, paresthesia, fatigue, and nausea
Rimegepant	No	Oral	acute	No FDA-approved dosing	Nausea and UTI Ubrogepant
Ubrogepant	No	Oral	acute	No FDA-approved dosing	Nausea and dizziness

AE indicates adverse effect; IV, intravenous; SC, subcutaneous; URI, upper respiratory infection; UTI, urinary tract infection.

4. CONCLUSION

We have covered the genetic and metabolic causes of migraine in this review. The frequency, intensity, and impact on quality of life of migraines, a chronic neurological disorder with multiple contributing factors, vary. A person's genetic composition greatly influences how susceptible they are to migraines. The pathophysiology of these patients emphasizes the existence of several triggers that either cause or intensify headache attacks. Options for treatment should take into account the patient's goals, preferences, and aspirations in addition to their symptoms, diagnosis, and any co-existing or comorbid diseases.

In conclusion, migraine is frequently underdiagnosed while being a common ailment. Additionally, some migraine patients who qualify for preventative therapy do not appropriately perceive it. These treatments have the potential to improve migraine sufferers' quality of life and lessen their functional and physical impairments.

In the upcoming years, more research and advancements are anticipated, which should help to further increase awareness of a complicated issue that affects millions of people worldwide.

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