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A DETAILED REVIEW ON COMPLETE UNDERSTANDING OF MIGRAINE AND ITS TREATMENT

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ABSTRACT:

Migraine is a disabling primary headache disorder that directly affects more than one billion people worldwide including children. Migraine is the third most prevalent illness in the world. Despite its widespread prevalence, migraine remains under-diagnosed and under-treated. There is very little known about migraine for several years, however in the last few decades, considerable advances in our understanding of migraine and its pathophysiology have paved the way for better understanding of the disease condition. Migraine is of several types among which Migraine with Aura, Migraine Without aura and chronic migraine are frequently seen among patients. Migraine has strong genetic component (80% of people with migraine tend to have familial histories of the disease.) and known triggers that induce pain. ICH–3 guidelines were used in diagnosis of Migraine and there are many acute and preventive migraine treatments that are proved to be effective in migraine. Acute treatment is either specific (triptans and ergots) or non-specific (analgesics). Preventive treatment decreases migraine frequency and improves quality of life. Recent advances led to development of newer classes of drugs like CGRP antagonists namely gepants and 5-HT 1F receptor agonists—namely ditans were also included. Despite of various pharmacological treatments available there is a strong need in clinical practice for alternative approaches for both acute and preventive treatment due to limited efficacy and poor toleration of pharmacological treatment in some patients.

This review tends to provide a complete overview of Migraine disorder that includes types, etiology, epidemiology, pathophysiology, ICH guidelines for diagnosis, current available Treatments of migraine with special emphasis of FDA approved novel drugs in last 5 years and also various non-pharmacological treatments available and lifestyle management of patients with Migraine.

Keywords: Migraine, Classification, Pathophysiology, Therapy, Novel Drugs, Non Pharmacological Therapy

1. INTRODUCTION:

Migraine is a primary episodic headache disorder characterized by various combinations of neurological, gastrointestinal, and autonomic changes. Migraine is derived from the Greek term hemicrania, which means "headache"(1).

- **Types of Migraine:**

1.1 Migraine without aura (Previously used terms: Common migraine; hemicranias simplex)

Recurrent headache disorder that is characterized by attacks lasting 4–72 hours involving unilateral location, pulsating quality, moderate or severe intensity, aggravated by normal physical activity, and associated with nausea, and/or photophobia and phonophobia (2)

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1.2 Migraine with aura (Previously used terms: Classic migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnee; complicated migraine.)

Recurrent attacks of unilateral completely reversible visual, sensory, or other central nervous system symptoms that would last several minutes often develop gradually and are followed by headache and related migraine symptoms. (2)

1.2.1 Migraine with Typical Aura

Migraine with aura is characterized by progressive development of a mix of positive and negative features, with complete reversibility, and consists of visual, sensory, and/or speech/language symptoms that last not more than one hour but have no motor weakness.

- **Typical aura with headache:** Migraine with typical aura, in which the aura is followed by a headache with or without migraine features within 60 minutes of the aura.

- **Typical aura without headache:** Migraine with a typical aura that is neither accompanied nor followed by any type of headache. (2)

1.2.2 Migraine with brainstem aura (Previously used terms: Basilar artery migraine)

Migraine with aura symptoms originating from the brainstem, but has no motor weakness. (2)

1.2.3 Hemiplegic Migraine

Migraine with aura including motor weakness. (2)

1.2.3.1 Familial hemiplegic migraine (FHM)

Migraine with aura including motor weakness, and at least one first- or second-degree relative has migraine aura including motor weakness. ·Mutations in the CACNA1A gene (calcium voltage-gated channel alpha 1A subunit) on chromosome 19p13 causes Type 1 FHM (3).

- Mutations in the ATP1A2 gene (ATPase, Na+/K+ transporting alpha 2 subunit) on chromosome 1q23 causes Type 2 FHM (4).

- Mutations in the SCN1A gene (sodium voltage-gated channel Type 1 alpha subunit) cause Type 3 FHM.

- PRRT2 (Proline-Rich Transmembrane 2) gene mutations have been identified as a possible cause (5). PRRT2 gene encodes a protein that interacts with SNAP25 (synaptosomal nerve-associated protein 25) and may play a role in the regulation of voltage-gated calcium channels(6).

- Mutations in the SLC4A4 (solute carrier family 4 member 4) gene have also been associated with familial forms of migraine(7).

1.2.3.2 Sporadic hemiplegic migraine (SHM)

Migraine with aura including motor weakness, and no first- or second-degree relative has migraine aura including motor weakness. (2)

1.2.4 Retinal migraine

A migraine headache is usually associated with repeated attacks of monocular visual disturbance, including scintillations, scotomata, or blindness. (2)

1.3 Chronic migraine

Headache that occurs 15 or more days per month for more than three months and exhibits the characteristics of a migraine headache on at least eight days per month. (2)

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1.4 Complications of migraine

- **Status migrainosus:** A debilitating migraine attack lasting for more than 72 hours.
- **Persistent aura without infarction:** Aura symptoms persisting for one week or more without evidence of infarction on neuroimaging.
- **Migrainous infarction:** One or more migraine aura symptoms occurring in association with an ischaemic brain
- **Migraine aura-triggered seizure:** A seizure triggered by an attack of migraine with aura. (2)

1.5 Probable migraine (Previously used term: Migrainous disorder)

Migraine-like attacks that do not meet all of the criteria for a type or subtype of migraine indicated above and do not meet the criteria for another headache disorder. (2)

1.6 Episodic syndromes that may be associated with migraine

- **Recurrent gastrointestinal disturbance:** Recurrent episodic attacks of abdominal pain and/or discomfort, nausea, and/or vomiting that occur infrequently, chronically, or at predictable intervals that may be associated with migraine.

- **Cyclic vomiting syndrome:** Recurrent episodes of severe nausea and vomiting, which are usually stereotypical in the individual and occur at the timing of episodes. Pallor and lethargy are two symptoms that may accompany an attack. Between attacks, all symptoms disappear completely.

- **Abdominal migraine:** An idiopathic disorder characterized by recurrent attacks of moderate to severe midline abdominal pain, accompanied by vasomotor symptoms, nausea, and vomiting, lasting 2–72 hours and with normality between episodes and are reported primarily in children. Headache does not occur during these episodes.

- **Benign paroxysmal vertigo:** A disorder characterized by recurrent brief attacks of vertigo in otherwise healthy children that happen without warning and resolve spontaneously.

- **Benign paroxysmal torticollis:** Recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously. The condition occurs in infants and small children, with onset in the first year. (2)

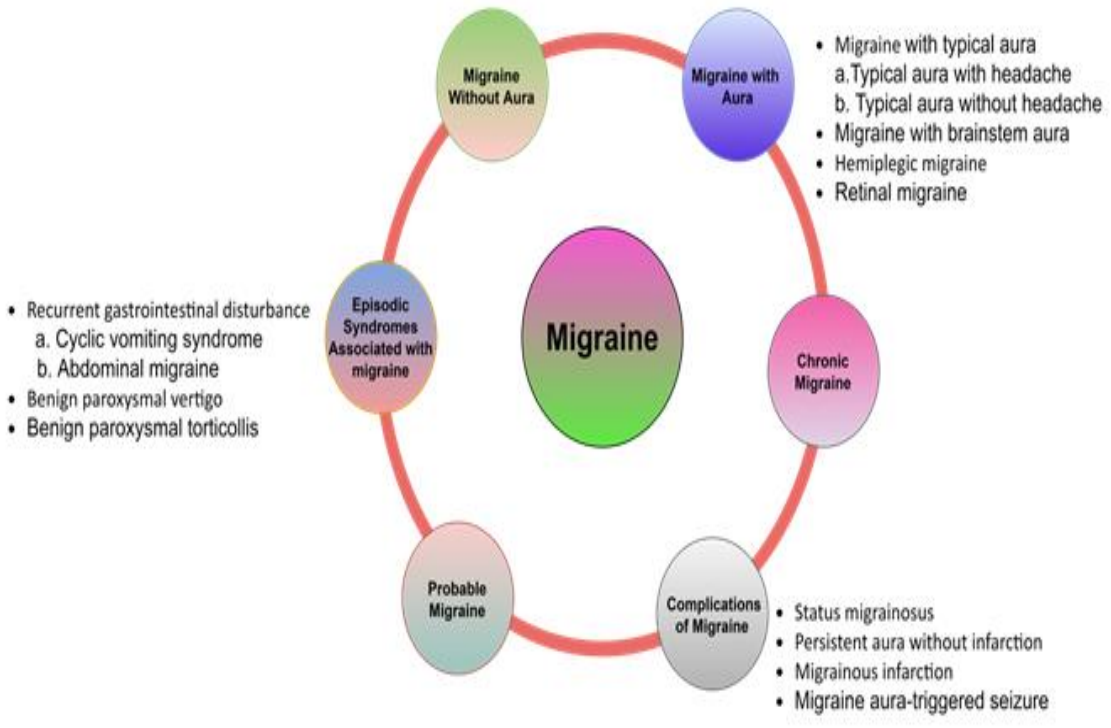

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Figure 1: Types of Migraine

1. Epidemiology:

Migraine is a very common neurological disorder that affects 39 million men, women, and children in the United States and 1 billion people throughout the world. Migraine is the third most prevalent illness in the world. Migraine affects 12% of the population, including children. Migraine affects the majority of people between the ages of 18 and 44. Migraine tends to run in families around 90% of migraine sufferers have a family history of the disease. Someone in the United States visits the emergency room every ten seconds with head pain, including 1.2 million visits for acute migraine headaches. While the majority of migraine sufferers only have episodes once or twice a month, over 4 million people suffer from chronic daily migraine, with at least 15 migraine days each month. Boys suffer from migraines more frequently than girls during childhood, but as adolescence approaches, the frequency of migraines increases more rapidly in females than in boys(8).

2. **Etiology:**

➢ **Genetics and Inheritance**

Migraine has a strong genetic component. The risk of migraines in ill relatives is three times greater than that of relatives of non-ill subjects, but there has not been any pattern of inheritance identified(9, 10). The genetic basis of migraine is complex, & it is uncertain which loci and genes are the ones implicated in the pathogenesis; it may be based on more than one genetic source at different genomic locations acting in tandem with environmental factors to bring susceptibility and the characteristics of the disease in individuals(11). The identification of these genes in an individual with migraines could predict the targeted prophylactic treatment.

➢ **MELAS**

Melas is a syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.
a multisystemic disorder by maternal inheritance that can present recurrent migraine headaches (12).

➢ **CADASIL**

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) angiopathy by autosomal dominant inheritance, caused by mutations in the NOTCH3 gene (notch receptor 3) on chromosome 19 that can present migraine with aura (prodrome in 80%) in nearly 50% of carriers (13)

➢ **RVCL**

Retinal vasculopathy with cerebral leukodystrophy is angiopathy by C-terminal frame-shift mutations in TREX1 (three prime repair exonuclease 1) presents almost 60% of the cases (14)

➢ **HIHRATL**

Hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy

➢ **HERNS**

Hereditary endotheliopathy with retinopathy, nephropathy, and stroke

➢ **Triggers**

Withdrawn or exposed to several factors contribute to the development of migraine headaches(15, 16) Some of them are probable factors that contribute, while others are only possible or unproven factors.

- Stress in 80% (probable factor)
- Hormonal changes in 65% during menstruation, ovulation, and pregnancy (probable factor)
- Skipped meals 57% (probable factor

3. Pathophysiology:

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Figure 2: Phases of Migraine Attack

5.1 PHASE 1: PREMONITORY

The Interplay between Alterations in Homeostasis and the Onset of Migraine:

- The migraine premonitory phase might start as early as three days before a migraine headache(17).
- Fatigue, mood changes, food cravings, yawning, muscle tenderness, and photophobia are a few symptoms that suggest that the hypothalamus, brainstem, limbic system, and certain cortical areas are being involved during the early stages of an attack (18-20).
- Migraine may also display a diurnal periodicity and is often induced by changes in homeostasis(21).
- These findings point to the role of chronobiological mechanisms in migraine pathogenesis, prompting researchers to look into the hypothalamus as a potential migraine attack origin site(19, 21).
- Functional neuroimaging studies provide evidence of the involvement of the hypothalamus during the premonitory phase. Activations were found in the posterolateral hypothalamus, midbrain tegmental area, periaqueductal gray, dorsal pons, and various cortical areas during the premonitory phase in a positron emission tomography study using cerebral blood flow as a marker of neuronal activity in patients with glyceryl trinitrate-induced migraine attacks(18).
- Two main theories for this mechanism exist; the first claims that increased parasympathetic tone activates meningeal nociceptors, while the second proposes that nociceptive signals from the trigeminal nucleus caudalis (TNC) to supratentorial regions involved in pain processing are modulated(23, 24).

Modulation of Nociceptive Signals from the Thalamus to the Cortex and the Threshold Set by Cyclical Brainstem Activity:

The release of excitatory and inhibitory neuropeptides/neurotransmitters from hypothalamic and brainstem neurons may regulate nociceptive trigeminovascular signals reaching the thalamus(19).

- Relay trigeminovascular neurons' firing is controlled by the balance of these neurotransmitters. The firing of thalamic trigeminovascular neurons can be shifted from burst to tonic mode if the neurotransmitter is excitatory, or from tonic to burst mode if the neurotransmitter is inhibitory(24).
- In migraine patients, the converging inputs from hypothalamic and brainstem neurons can establish high and low setpoints for the allostatic load (the amount of physiological or emotional stress that the brain can manage) and hence determine whether nociceptive signals are delivered to the cortex(19, 27).
- The current circadian phase of cyclical brainstem activity may also influence whether the premonitory phase changes into the headache phase (19, 20, 27, 28).
- When cyclical brainstem activity is high, the threshold for nociceptive trigeminovascular signal transmission is elevated, & nociceptive signals are blocked. When cyclical brainstem activity is low, the threshold for transmitting nociceptive signals is decreased, & a migraine headache may occur(19, 27).

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5.2 PHASE 2: AURA

- Aura is observed in around one-third of migraine attacks(29).
- Migraine with aura is defined by the International Classification of Headache Disorders 3rd edition (ICHD-3) as recurring attacks of unilateral, fully reversible visual, sensory, or other CNS symptoms that develop gradually and are usually followed by headache and other migraine symptoms(30)
- Visual disturbances are the most common aura symptom; however, sensory, speech/language, and motor disorders, as well as disruption of higher cerebral function, are also common (30, 31).

Initiation and Propagation of Cortical Spreading Depression (CSD):

- CSD was first described by Aristides Leao in 1944 and is believed to be the neurophysiological correlate of migraine(32, 33).
- It is characterized by a slowly (2-6 mm/min) propagating wave of depolarization in neuronal and glial cell membranes that is followed by inhibition of cortical activity for up to 30 minutes, along with the initiation and progression of aura symptoms(Fig. 2)(33-36).
- This wave of spreading depression is also accompanied by a wave of hyperemia, which is followed by a prolonged period of cortical oligemia(37, 38).
- Localized increases in extracellular potassium (K+) cause persistent depolarization of neurons for 30-50 seconds, causing CSD(35).
- It's been proposed that extracellular K+ accumulates as a result of recurrent depolarization and repolarization of hyperexcitable neurons in the cerebral cortex and that this extracellular K+ accumulation further depolarizes the cells from which it was released(33, 35, 39).
- This substantial K+ efflux is linked to a major disturbance of cell membrane ionic gradients, sodium (Na+) and calcium (Ca2+) influx, and glutamate release(40).
- CSD propagation is still a mystery, and numerous theories have been proposed. The propagation of CSD was originally considered to be mediated by interstitial diffusion of either K+ or glutamate, but later hypotheses imply that it is mediated by gap junctions between glial cells or neurons(34).
- Animal research is increasingly supporting the idea that CSD can activate trigeminal nociception and so trigger headache mechanisms (33, 41, 42).
- The characteristic throbbing pain of migraine headache is a result of trigeminovascular pathway activation. The trigeminovascular pathway is widely understood and its anatomy and physiology explain how migraine pain is distributed(19).

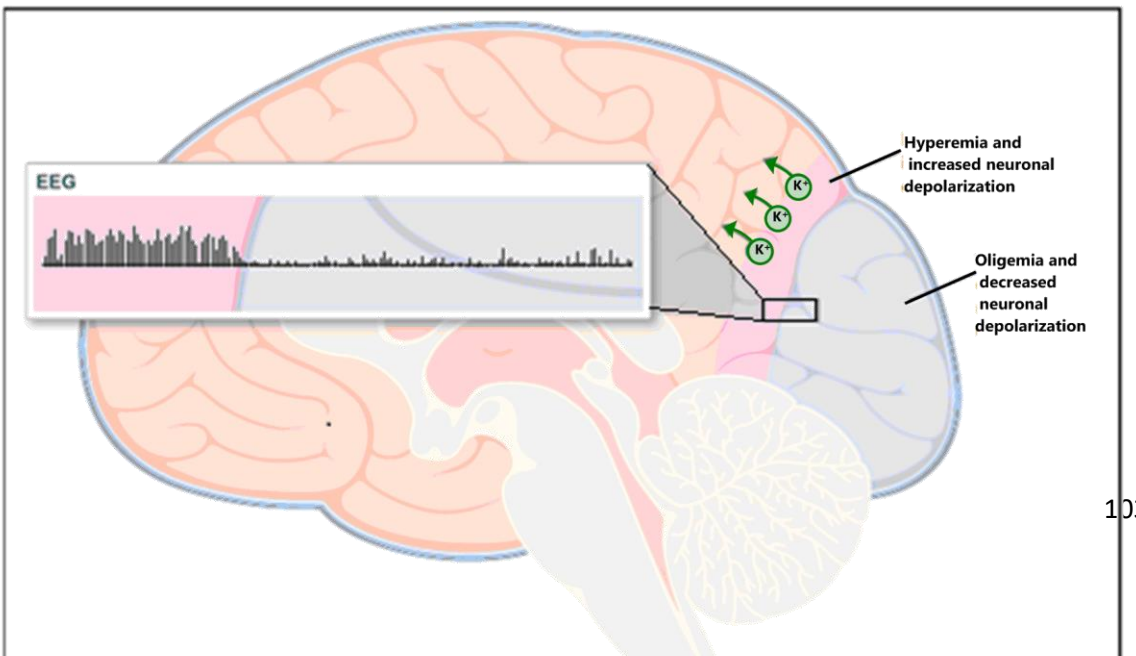

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Figure 4: Spreading of Cortical Depression EEG = electrocardiogram; K^+ = Potassium

The Trigeminovascular Pathway:

- Nociceptive information is sent from the meninges to the central areas of the brain, and then to the cortex, via the trigeminovascular pathway. The meninges and major cerebral arteries are innervated by nociceptive fibres that originate in the trigeminal ganglion(19, 28). This nociceptive innervation occurs mainly through the ophthalmic branch of the trigeminal nerve(28).

- Before synapsing on second-order neurons in the trigeminal cervical complex (TCC), which includes the TNC and the dorsal horn of the upper cervical spinal cord (C1-C2), afferent projections from the trigeminal ganglion converge with inputs from adjacent skin, pericranial and paraspinal muscle, and other C1-C2 innervated tissues(28, 29, 43-45).

- Referred pain perception in the periorbital, occipital, and cervical-neck areas is caused by the convergence of afferent projections with neurons from extracranial structures(44).

- Multiple brainstem, thalamic, hypothalamic, and basal ganglia nuclei receive signals from ascending pathways from the TCC(46).

- These nuclei project to a variety of cortical areas, including the somatosensory, insular, motor, parietal association, retrosplenial, auditory, visual, and olfactory cortices, which are involved in processing the cognitive, emotional, and sensory-discriminative aspects of nociceptive signals and cause symptoms like photophobia, phonophobia, cognitive dysfunction, osmophobia, and allodynia. (Fig. 3)(19, 47).

- The trigeminovascular pathway is activated by nociceptive neurons that innervate the dura mater, which release vasoactive neuropeptides like calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide-38, causing signaling along the trigeminovascular pathway – the extent to which arterial vasodilation, mast cell degranulation, and plasma extravasation are involved remains unclear(48-50).

- CSD is thought to trigger the activation of meningeal nociceptors(33). Locally produced molecules such as ATP, glutamate, K1, hydrogen ions, CGRP, and nitrous oxide are thought to diffuse toward and activate meningeal nociceptors during a CSD(29).

- However, the majority of migraine episodes, on the other hand, are not preceded by clinical symptoms of aura; aura can come after the headache phase has already begun, and patients can have an aura but not the subsequent headache(38).

- Many patients reported migraine symptoms such as nausea (51 percent), photophobia (88 percent), phonophobia (73 percent), and headache (73 percent) during the aura phase, and 11 percent reported the headache starting simultaneously with the aura in a prospective study of the time course of aura and headache symptoms(13).

- So, it has been proposed that aura is the result of an abnormal "brain state" that occurs during a migraine attack in a genetically susceptible individual and those physiological events occurring during the premonitory phase (which occurs before aura) are the primary cause of both trigeminovascular pathway activation and cortical neuronal/glial activity(18, 38).

Peripheral Sensitization:

- Peripheral trigeminovascular neurons get sensitized to dural stimuli after being engaged by endogenous mediators, which means their response threshold falls and the magnitude of their response increases(19).

- The characteristic throbbing pain of migraine, as well as the worsening of pain by leaning over or coughing, is thought to be caused by peripheral sensitization(19).

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- Hyperresponsiveness within primary afferent fibres and/or central neurons is assumed to be the origin of this enhanced sensitivity to a sensory stimulus(33).

- Mast cell degranulation causes long-term activation and sensitization of dural nociceptors, according to rat studies of trigeminovascular activation(51).

- CGRP release has been linked to the development and maintenance of peripheral sensitization in several animal studies(52, 53). The response threshold to a painful mechanical stimulation was significantly reduced as a result of peripheral sensitization in a study of rats with repeated CGRP injections into their paws(53).

4. Treatment:

4.1 Acute Treatment:

The following are some of the goals of the acute treatment of migraine patients:(56)

- To provide rapid and consistent freedom from pain and associated symptoms, especially the most bothersome symptom, without recurrence.
- To Minimize the need for repeat dosing or rescue medications.
- Optimal self-care and reduced subsequent use of resources (e.g., emergency room visits, diagnostic imaging, clinician and ambulatory infusion center visits).
- To minimize or prevent adverse events (AEs).
- To restore the normal functioning.

4.1.1 Indications

A trial of acute pharmacological and/or non-pharmacologic treatment should be offered to all patients with a confirmed diagnosis of migraine.

Table 1: Medications Used in Acute Treatment of Migraine

Drug class	Drug	Dosage and route	Contraindications
First-line medication			
NSAIDs	Acetylsalicylic Acid	900–1,000 mg oral	Gastrointestinal bleeding, heart failure
	Ibuprofen	400–600 mg oral	
	Diclofenac Potassium	50 mg oral (soluble)	
Other simple Analgesics (if NSAIDs are Contraindicated)	Paracetamol	1,000 mg oral	Hepatic disease, renal failure
Antiemetics(when necessary)	Domperidone	10 mg oral or suppository	Gastrointestinal bleeding, epilepsy, renal failure, cardiac arrhythmia
	Metoclopramide	10 mg oral	Parkinson disease, epilepsy,
Second-line medication			

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Triptans	Sumatriptan	50 or 100 mg oral or 6 mg SC or 10 or 20 mg intranasal	Cardiovascular or cerebrovascular disease, uncontrolled hypertension, hemiplegic migraine, migraine with brainstem aura
	Zolmitriptan	2.5 or 5 mg oral or 5 mg intranasal	
	Almotriptan	12.5 mg oral	
	Eletriptan	20, 40 or 80 mg oral	
	Frovatriptan	2.5 mg oral	
	Naratriptan	2.5 mg oral	
	Rizatriptan	10 mg oral tablet (5 mg if treated with propranolol) or 10 mg mouth-dispersible Wafers	
Third-line medication			
Gepants	Ubrogepant	50, 100 mg oral	Co-administration with strong CYP3A4 nhibitors
	Rimegepant	75 mg oral	Hypersensitivity, hepatic impairment
Ditans	Lasmiditan	50, 100, or 200 mg oral	Pregnancy, concomitant use with drugs P-glycoprotein substrates

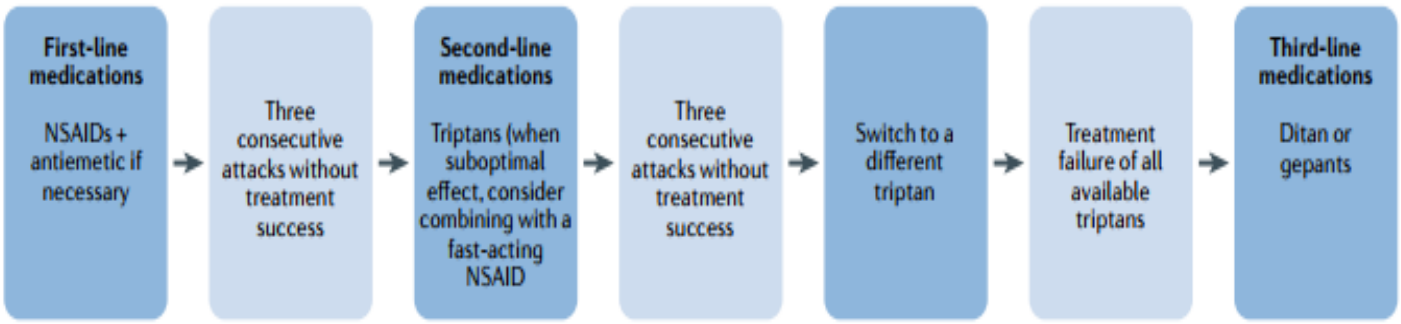

Figure 6: Acute Treatment of Migraine

Effective Acute treatment can help to alleviate the pain, associated symptoms, and impairment that come with attacks. Suboptimal acute treatment is linked to more migraine-related impairment and a higher risk of illness progression (56).

- **First-line medication:** In the treatment of acute migraines, over-the-counter analgesics are extensively used. Non–steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective, and the strongest evidence supports the use of acetylsalicylic acid, ibuprofen, and diclofenac potassium as first-line medications (57-59). Paracetamol is ineffective and should only be used by people who are intolerant to NSAIDs(60)

- **Second-line medication:** Patients who do not get adequate relief from over-the-counter analgesics should be prescribed a triptan. Although all triptans have been shown to be effective, their availability and accessibility

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vary by country. When taken early in an attack, when the headache is still moderate, triptans are most beneficial(61, 62)**.** However, there is no evidence that triptans should be used during the aura phase of a migraine attack. Even if one triptan is ineffective, others may still be able to assist to provide relief(63, 64). Sumatriptan via subcutaneous injection can be effective when all other triptans have failed, especially in patients who rapidly reach peak headache intensity or are unable to take oral triptans due to vomiting(65). Relapses, which are defined as the return of symptoms within 48 hours of an apparently successful treatment, can occur in some people. Patients can repeat their triptan treatment or augment it with fast-acting formulations of naproxen sodium, ibuprofen lysine, or diclofenac potassium if they experience a relapse(66, 67). Patients should be advised, however, that repeating the treatment does not prevent additional relapses and, in turn, increases the risk of MOH.

- **Third-line medication:** Alternatives are currently limited, if all available triptans fail after an adequate trial period (no or insufficient therapeutic response in at least three consecutive attacks) or if their usage is contraindicated. Ditans or gepants could be used, and they're hard to get by right now. The only ditan approved for acute migraine treatment is lasmiditan, while the only gepants approved are ubrogepant and rimegepant. The efficacy of lasmiditan is comparable to that of triptans, according to an indirect comparison of data from randomized control trials,(68-70) but its use is associated with temporary driving impairment, which is likely to discourage widespread use.

  Individuals using lasmiditan should not drive machinery for at least 8 hours after taking it since they may be unable to self-assess their driving ability. Medications that are used in addition to the main medications include Prokinetic antiemetics such as domperidone and metoclopramide are excellent oral adjuncts for patients who have nausea and/or vomiting during migraine attacks.

- **Medications to avoid:** Oral ergot alkaloids are ineffective and potentially dangerous, thus they should not be used in place of triptans(71). The efficacy of opioids and barbiturates is questionable, and both are associated with considerable adverse effects and the risk of dependency(72). As a result, all of these medications should be avoided in the treatment of acute migraine.

6.2 Preventive treatment

The goals of migraine prevention are :(56, 73, 74)

- To improve health-related quality of life (HRQoL).
- To improve function and reduce disability.
- To reduce attack frequency, severity, duration, and disability.
- To improve responsiveness to and avoid escalation in the use of acute treatment.
- To reduce reliance on poorly tolerated, ineffective, or unwanted acute treatments and to reduce cost.
- To enable patients to manage their disease to enhance a sense of personal control.
- To reduce headache-related distress and psychological symptoms.

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Table 2: Considerations for Preventive Treatment:

Prevention should be …	Headache days/ month	Degree of disability required
Offered	6 or more	None
	4 or more	Some
	3 or more	Severe
Considered	4 or 5	None
	3	Some
	2	Severe

- **Initiation and termination:** Additional preventive therapy should be explored in patients whose migraine continues to impair their quality of life despite optimal acute therapy (Table 4)**.** In practice, people who are considered for preventative treatment are adversely affected at least two days per month, though this is not an absolute rule(75). Clinicians should constantly evaluate characteristics such as the severity of attacks, the duration of attacks (for example, menstruation-related attacks tend to persist longer), and migraine-related disability in addition to migraine frequency. Overuse of acute medications is another reason for preventative therapy. The effectiveness of preventive therapy is rarely recognized instantly. Efficacy can only be determined after several weeks or months, thus patients should be discouraged from stopping treatment due to apparent inefficacy in the early stages(75). If an oral preventive medication's therapeutic dose is ineffective after 2–3 months, an alternative should be considered (75-77).

- For monoclonal antibody treatments that target calcitonin gene-related peptide (CGRP) or its receptor, efficacy should be assessed only after 3–6 months. The efficacy of onabotulinumtoxinA should be evaluated after 6–9 months.

Table 3: First–line Medications Used in Preventive Treatment

Drug class	Drug	Dosage and route	Contraindications
First-line medication			
Beta-blockers	Atenolol	25–100 mg oral twice daily	Asthma, cardiac failure, Raynaud disease, atrioventricular block, depression
	Bisoprolol	5–10 mg oral once daily	
	Metoprolol	50–100 mg oral twice daily or 200 mg modified-release oral once daily	

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	Propranolol	80–160 mg oral once or twice daily in long-acting formulations	
Angiotensin II-receptor blocker	Candesartan	16–32 mg oral per day	Co-administration of aliskiren
Anticonvulsant	Topiramate	50–100 mg oral daily	Nephrolithiasis, pregnancy, lactation, glaucoma

Table 4: Second–line Medications Used in Preventive Treatment

Drug class	Drug	**Dosage and route**	**Contraindications**
Second-line medication			
Tricyclic antidepressant	Amitriptyline	10–100 mg oral at night	Age <6 years, heart failure, co-administration with monoamine oxidase inhibitors and SSRIs, glaucoma
Calcium antagonist	Flunarizine	5–10 mg oral once daily	Parkinsonism, depression
Anticonvulsant	Sodium valproate	600–1,500 mg oral once daily	Liver disease, thrombocytopenia, female and of childbearing potential

Table 5: Third–line Medications Used in Preventive Treatment

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Drug class	Drug	Dosage and route	Contraindications
Third-line medication			
Botulinum toxin	OnabotulinumtoxinA	155–195 units to 31–39 sites every 12 weeks	Infection at the injection site
Calcitonin gene-related peptide monoclonal antibodies	Erenumab	70 or 140 mg subcutaneous once monthly	Hypersensitivity Not recommended in patients with a history of stroke, subarachnoid hemorrhage, coronary heart disease, inflammatory bowel disease, chronic obstructive pulmonary disease or impaired wound healing
	Fremanezumab	225 mg subcutaneous once monthly or 675 mg subcutaneous once quarterly	
	Galcanezumab	240 mg subcutaneous, then 120 mg subcutaneous once monthly	
	Eptinezumab	100 or 300 mg intravenous quarterly	

6.3 Chronic or Refractory Migraine Management

- Patients with chronic migraine frequently have various comorbidities that contribute to migraine chronification or disability, as well as poor lifestyle choices(78). Factors that may contribute to migraine chronification or persistence are presented in Box 4.

- In patients with refractory migraine, a combination of preventive interventions may be used(79). This is especially true if a treatment is effective but comes with unpleasant side effects. Topiramate, for example, may help to avoid weight gain induced by other preventatives. In patients with chronic migraine, onabotulinum toxin A may also be added(80).

- When starting onabotulinum toxin treatment, it is not necessary to stop taking other preventatives that are only partially effective.

Potentially modifiable factors that contribute to migraine chronification or persistence:

- High frequency of headache attacks
- Poor response to acute treatment
- Medication overuse
- Excessive caffeine intake
- Obesity
- Obstructive sleep apnea
- Stressful life events
- Mood disorders

6.4 Management of Migraine in Special Populations:

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- **Older people**

Migraine generally remits as people become older, but the prevalence of various secondary headaches rises.(81) Hence, the onset of apparent migraine after the age of 50 should raise suspicions of an underlying aetiology. Clinical management of migraine sufferers who have had migraines since childhood is generally unchanged in practise.
The use of triptans in elderly persons, for instance, is frequently discouraged due to the high probability that these patients have cardiovascular disease and/or risk factors. However, there is no strong evidence that triptan use increases the risk of cerebrovascular or cardiovascular events in older persons.(82)

- **Children and Adolscents :**

Migraine episodes in children and adolescents differ from those in adults in that they are generally shorter, the headache is more often bilateral and less often pulsating, and gastrointestinal symptoms are more common.(75) Clinical management of children and young adolescents usually necessitates active participation from family members and teachers, therefore both must be educated. In children who have short-term attacks, bed rest alone may be sufficient. Ibuprofen, at a dose adequate for body weight, is advised as a first-line medicine when needed.(83) Domperidone can be used to treat nausea in adolescents aged 12 to 17 years, while it is unlikely to prevent vomiting if taken orally. Multiple NSAIDs and triptans have been approved for the acute treatment of migraine in adolescents aged 12–17 years, with some evidence suggesting that nasal spray formulations of sumatriptan and zolmitriptan are the most efficacious.(75)

- **Pregnant and breastfeeding women:**

Migraine usually remits during pregnancy, but if medication is continued, the risk of harm to the foetus must be taken into account.(84) Despite its low effectiveness, paracetamol should be used as the first-line treatment for acute migraine in pregnancy.(60); NSAIDs can be used only during the second trimester.(85) Because the safety data available is limited and comes from post-marketing surveillance, triptans should only be taken under the direct supervision of a specialist. The majority of the data pertains to the usage of sumatriptan.(75) Metoclopramide can be used to treat nausea caused by migraines during pregnancy.(86)

6.5 Non-Pharmacological Therapy:

Alternative approaches to acute and preventive treatment, in addition to pharmacological treatments, are in high demand in clinical practice. This need may arise in the case of low-frequency migraneurs who are unwilling to utilize medication or are concerned about potential negative effects. At the opposite end of the spectrum, clinicians are confronted with patients who have shown refractory to multiple drugs. Nutraceuticals, Behavioural Therapies, Acupuncture, and Neuromodulation techniques are examples of nonpharmacologic treatments with evidence of efficacy for migraine prevention(87)

6.5.1 Nutraceuticals

Riboflavin and magnesium, in particular, are effective options for individuals with comorbidities who are taking many drugs or who are unable to tolerate pharmacological side effects. They're also inexpensive and widely available(87)

6.5.2 Behavioral Techniques and Acupuncture:

Behavioral treatment approaches can be used in conjunction with ongoing treatments and can often result in clinical improvement.

- Relaxation training
- Biofeedback
- Cognitive-behavioral therapy

6.5.3 Non-invasive neuromodulation:

Non-invasive neuromodulation constitutes a valuable approach with strong backing evidence, particularly in the case of sTMS and transcutaneous cranial nerve stimulation. It is however available only in specialized centers, of several, but not most, countries. Different techniques include: (81)

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- Transcutaneous Cranial Nerve Stimulation
- Non-Invasive Vagus Nerve Stimulation (nVNS)
- Single-Pulse Transcranial Magnetic Stimulation (sTMS)
- Transcranial Direct Current Stimulation (tDCS)
- Percutaneous Mastoid Stimulation
- Non-Painful Brachial Electric Stimulation

6.5.4 Invasive Neuromodulation:

On the other hand, Implantable neuromodulation devices should only be possibly considered for the most serious and refractory patients who have failed multiple preventive attempts.

- Occipital Nerve Stimulation (ONS)
- Sphenopalatine Ganglion Stimulation (SNS)
- High Cervical Spinal Cord Stimulation(87)

6.6 Lifestyle management:

Regular exercise, enough hydration, eating regular meals, and avoiding recognized triggers are all good lifestyle behaviors that can help minimize headache frequency(89, 90). Sleep has the most impact of all of them, thus any patient with bothersome headaches should have their sleep duration and quality checked(91).

Migraine Surgery: There is a growing body of evidence suggesting that migraine surgery patients have a high rate of success. Patients who have not responded to medical or pharmacologic treatments but have a positive response to BTX-A or local anesthetic injections at trigger sites are the best candidates for migraine surgery. The trigger sites are released to treat migraine headaches. The trigger sites are as follows:(101)

a. Frontal – Release of Supraorbital, Supratrochlear, and Zygomaticofacial nerves
b. Temporal – Neurectomy of Zygomaticotemporal(ZTN) and Auriculotemporal nerves(ATN)
c. Occipital – Release of greater occipital, lesser occipital and third occipital nerves
d. Rhinogenic – Septoplasty, and Turbinectomy are procedures performed to relieve intranasal contact points that impinge on the trigeminal nerve's terminal branches.

6.7 New FDA approved drugs for Migraine in last 5 years:

Following are the FDA approved novel drugs in last 5 years for migraine(102)

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Drug Class	Name	Pharmaceutical Company	Brand Name	FDA Approval	Indication
CGRP antagonist	Atogepant	ABBVIE INC	Qulipta	9/28/2021	To prevent episodic migraines
CGRP antagonist	Rimegepant	BIOHAVEN IRELAND	Nurtec ODT	2/27/2020	To treat migraine
CGRP antagonist	Eptinezumab-jjmr	Lundbeck Seattle BioPharmaceuticals Inc.	Vyepti	2/21/2020	For the preventive treatment of migraine in adults
CGRP antagonist	Ubrogepant	ALLERGAN	Ubrelvy	12/23/2019	To treat acute treatment of migraine with or without aura in adults
Serotonin (5-HT) 1F receptor agonist	lasmiditan	ELI LILLY AND CO	Reyvow	10/11/2019	For the acute treatment of migraine with or without aura, in adults
CGRP antagonist	Galcanezumab-gnlm	ELI LILLY AND CO	Emgality	9/27/2018	For the preventive treatment of migraine in adults
CGRP antagonist	Fremanezumab-vfrm	TEVA PHARMS USA	Ajovy	9/14/2018	For the preventive treatment of migraine in adults
CGRP receptor antagonist	erenumab-aooe	AMGEN INC	Aimovig	5/17/2018	For the preventive treatment for migraine

CGRP = Calcitonin Gene Related Peptide

CONCLUSION:

Migraine is a common neurological disorder that contributes significantly to the global disease burden. Despite the existence of comprehensive diagnostic criteria and a plethora of therapeutic options, migraine diagnosis and clinical management remain suboptimal globally. This Consensus Statement was developed by European experts to provide generally applicable recommendations for migraine diagnosis and management, as well as to promote best clinical practises. The recommendations are based on published evidence and expert opinion, and they will be updated as new data and treatments become available.

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