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Review Article

A Review on Migraine

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Abstract

Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Migraine, the second most common cause of headache and indeed neurologic cause of disability in the world and attacks lasting 4-72 hours, of a pulsating quality, moderate or severe intensity aggravated by routine physical activity and associated with nausea, vomiting, photophobia or phonophobia. Migraine has multiple phases: premonitory, aura, headache, postdrome, and interictal. The primary cause of a migraine attack is unknown but probably lies within the central nervous system. Migraine can occur due to various triggering factors and can be managed with both pharmacological and non-pharmacological treatment. Migraine attacks are treated with nonsteroidal anti-inflammatory drugs (NSAIDS), or triptans. Non-pharmacological treatment includes cognitive behavioural therapy, Complementary Treatments, yoga therapy etc.

Keywords: Migraine; NSAIDS; Therapy

Introduction

Headache disorders, this are characterized by the recurrent episodes of headache and are the most common nervous system disorders. Headache itself is the painful and also disabling feature of few numbers of primary headaches, like migraine, cluster headache, tension type headache. Among these, the migraine headache is ubiquitous, prevailing, disabling and essentially treatable, but still under-estimated and under-treated [1].

Migraine is the second most cause of headache and the most common headache related and neurologic cause of disability in the world [2]. The name 'migraine' comes originally from the Greek word 'hemicrania', it means 'half of the head', it represents one of the most important features of the condition, that in many of the cases, the pain will affects half of the head only. However sometimes the pain is felt bilaterally, either at back or front of the head and sometimes rarely all over the body and face ('migrainous corpalgia'). The pain is generally throbbing, and sometimes pulsatile in nature and it typically increases by any form of movements made by the body or head [3].

Migraine is a common chronic headache disorder which is characterized by the recurrent attacks which lasts from 4-72 hours, with a pulsating quality. Migraine is the commonest cause of headache and its intensity includes as mild, moderate and severe, it is aggravated by any of the routine physical activity. Migraine has some associated features like, vomiting, nausea, photophobia and/or phonophobia and migraine is attributed to the activation of meningeal perivascular pain fibers and also increased sensitization of central pain neurons that process information from intracranial structures and extra cranial skin and muscles [4,5].

Triggers for migraine

A number of intrinsic or extrinsic factors can trigger migraine attack. A migraine trigger is any environmental, dietary, or physiologic factor that can provoke migraine activity in the brain [6]. In different regions the social and cultural factors can vary thereby influencing the significance of triggering factors. There are only too little studies from India on migraine triggers. It is very important to have sufficient information or knowledge about the migraine triggers for the proper management of the patients [5].

Environmental triggers	Odours, bright lights, noise, and other excessive sensory stimuli. Painful stimuli that trigger migraine usually occur in the head and neck. The most common of these are neck injury and spasm, temporomandibular joint pain, and sinus inflammation. 40% of migraineurs report that they are affected by weather changes.
Food triggers	1. Byproducts of food aging are found in fermented products like red wine, aged cheeses, 2. and yeast in fresh bread and yogurt. 3. Foods with chemicals similar to the neurotransmitters that our brains use are coffee, chocolate, MSG, and the nitrates used as preservatives in many of our prepackaged foods.
Physiologic triggers	Stress, fatigue, lack of sleep, or alter their sleep schedule, sleeping too much, hunger, exercise, pain, hormone changes, like the drop in estrogen levels before the menstrual period or after menopause [6].

Table 1

Pathophysiology

Migraine is considered as the major common paroxysmal neurovascular disorder by the World Health Organization. The exact cause of a migraine attack is not known but it probably lies within the central nervous system [7].

Migraine is characterized by multiple phases: premonitory, aura, headache, postdrome, and interictal [8].

Premonitory phase

The premonitory phase begins as early as 3 days before the headache phase, and involves a complex interplay between various cortical and subcortical brain regions, including the hypothalamus and brainstem nuclei that modulate nociceptive signalling [8].

Migraine attacks are often come before by premonitory symptoms. Possible premonitory symptoms were included concentration problems, depression, food craving, physical hyperactivity, irritability, nausea, phonophobia, fatigue, sleep problems, stressed feeling, stiff neck and yawning [7].

Examination of symptoms that are most commonly described by patients point based on the involvement of the hypothalamus, symptoms like fatigue, depression, irritability, food cravings, and yawning, Brainstem, symptoms like muscle tenderness and neck stiffness, Cortex, symptoms like abnormal sensitivity to light, sound, and smell, and Limbic system, symptoms like depression and anhedonia, in prodromal phase of a migraine attack [9].

The premonitory phase includes

1. The Interplay Between Alterations in Homeostasis and the Onset of Migraine.
2. Activation of Meningeal Nociceptors by Increased Para sympathetic Activity.
3. Modulation of Nociceptive Signals from the Thalamus to the Cortex and the Threshold Set by Cyclical Brainstem Activity [8].

Aura phase

In one- third of patients, an aura phase may occur during some attacks and likely correlates with a cortical spreading depression-like event; a slowly propagating wave of neuronal and glial cell depolarization and hyperpolarization [8].

Wolff's vascular theory of migraine

The vascular theory of migraine was developed by the Neurologist, Harold G. Wolff, MD, in 1940s and he hypothesized that migraine attacks are caused by vasoconstriction in the cranial vasculature leading to oligemia and the reduction in the cerebral blood flow generate an aura. Compensatory vasodilation which occurs in the intracranial or extracranial blood vessels after the vasoconstriction was supposed to result in perivascular edema and inflammation which in turn triggers the headache pain [10].

In this vascular theory, he identified that "all pain is an action violated" and the pain which is due to headache is caused by vasodilation of both the cerebral and meningeal arteries [11]. and most of the brain is insensitive to pain, meningeal blood vessels are highly innervated by pain fibers. Blood vessel dilation was presumed to activate the trigeminal sensory nerves that surround the meningeal blood vessels, causing pain. There is no correct information or correlation between changes in the blood flow and also migraine symptoms, so thus some doubts raised about the vascular aetiology of migraine and the neural theory was opened [12].

The neuronal hyperexcitability at the onset of cortical spreading depression

It has been found that in addition to the classical electrical and mechanical triggers, the phenomenon can be induced by the increased extracellular potassium, glutamate, and inhibition of Na/K adenosine triphosphatase (ATPase) and in the interstitial space

potassium elevated by intense neuronal activity that led to the depolarization and excitation of adjacent Neurons, which in turn are "thrown into intense activity and liberate more K." Thus, as an alternative to the potassium hypothesis, neuronal synchronization and field oscillations that precede the front of depolarization play a critical role in extending the zone of depressed activity. The synchronization has been hypothesized to be caused by the non-synaptic interactions between neurons which are possibly mediated by the excitatory neurotransmitter, glutamate and/or through gap junctional interactions. These ideas are intriguing given the recent demonstration that in astrocytes the calcium signalling may lead to the induction of epileptiform hypersynchronous activity in adjacent neuronal networks and as a result, from astrocytes glutamate is released [10].

Cortical spreading depression

Aristides Leão, a Brazilian neurophysiologist doing his doctoral research on epilepsy at Harvard University, was first described the cortical spreading depression, is an electrophysiological event in the year 1943 [11].

Cortical spreading depression (CSD) is becoming increasingly accepted as the likeliest basis for the migraine aura and the trigger for headache pain and with massive efflux of potassium ions from intracellular to extracellular compartments CSD is characterized by rapid and nearly complete depolarization of a sizable population of cortical neurons. This process represents a regenerative all-or-none process that propagates slowly as a wave in the brain tissue. Before or during the development of a migraine headache a transient neurological disturbance called migraine aura appears shortly and aura commonly arises in the primary visual cortex with a characteristic distribution of fortification figures, it involves spreading scintillating scotomata. It is hypothesized that the intrinsic neurophysiologic events occurring in the brain during CSD irritate axon collateral nociceptors in pia and dura mater leading to trigeminal and parasympathetic activation. Trigeminal pain afferents originating in the meningeal vessels pass through the trigeminal ganglion and synapse on second-order neurons in the trigeminocervical complex. These nociceptive neurons, in turn, project through the trigeminal nucleus and, after decussating in the brainstem, form synapses with neurons in the thalamus. While migraine with aura is believed to originate in the neocortex, hippocampal spreading depression can also activate the trigeminal nucleus [10].

Cortical hyperexcitability in migraine

The precise trigger for migraine attacks is enigmatic. As it is the case for many episodic disorders, the trigger for migraine attacks has not been precisely identified. Many clinical factors such as diet, alterations in sleep and stress are known to predispose individuals to attacks. It is particularly intriguing that photic stimulation can trigger both migraine attacks and epileptic seizures. How these factors bring on a migraine attack is not known. However, there is evidence for enhanced cortical responsiveness to diverse stimuli in migraineurs. The techniques that have been used to generate this evidence include psychophysical studies; visual, auditory, and somato sensory evoked potentials; magneto encephalography; and transcranial magnetic stimulation of the motor cortex. In all cases, there is evidence of heightened reactivity between migraine attacks. Results from transcranial magnetic stimulation of the occipital (visual) cortex have been particularly compelling. Most but not all studies have observed that migraineurs have a reduced threshold for induction of phosphenes (the experience of light with non-luminous stimulation) compared with controls. This phenomenon appears to be equally present in individuals who experience migraines with and without aura. Thus, a pathologically low threshold for activation of cortical hyper excitability may characterize migraine [1].

Headache phase

The Trigeminovascular Pathway

The headache phase involves activation of the trigeminovascular system, a pathway that is well characterized. The characteristic throbbing pain of migraine headache is widely accepted to be the result of trigeminovascular pathway activation. The trigeminovascular pathway is well characterized and its anatomy and physiology explain the distribution of pain seen in migraine [8].

The trigeminovascular system (TGVS) consists of the trigeminal nerve and nerve fibers which innervate the network of extra- and intra- cranial meningeal blood vessels and the brain stem. This system is thought to play an integral role in regulating vascular tone and in the transmission of pain signals. Activation of this system during the pain phase of migraine is thought to initiate a cascade of chemical activity from trigeminal sensory nerve endings. Component trigeminal sensory nerves of this system store several vasoactive neuropeptides including: substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin A, nitric oxide (NO) and pituitary adenylate cyclase-activating peptide (PACAP) that upon

being released lead to inflammation and dilation of blood vessels aggravating the pain. Neuropeptides are important molecules that cause vasodilation and increase blood flow leading to edema in the meningeal vasculature as well as an inflammatory response around vascular structures in the meninges which is believed to be responsible for head pain. Precisely the peripheral terminations of the TGVS are located in correspondence of the extracranial soft tissues, such as muscles, eye, ear, skin, subcutaneous tissue, nasal cavities, arteries, periosteum, and also of intracranial structures, or venous sinuses, vagus and glossopharyngeal nerves [11].

The trigeminovascular pathway includes:

- **Activation of the Trigeminovascular Pathway:** The activation of migraine pain begins peripherally when nociceptive neurons that innervate the dura mater are stimulated and release vasoactive neuro- peptides such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide-38, causing signaling along the trigeminovascular pathway - the extent to which arterial vasodilatation, mast cell degranulation and plasma extravasation are involved remains unclear. Some believe that CSD initiates the activation of meningeal nociceptors [8].

- **Central Sensitization:** Central sensitization refers to a state in which nociceptive neurons in the spinal and medullary dorsal horn exhibit increased excitability, increased synaptic strength, and enlargement of their receptive fields beyond the original site of inflammation or injury. Peripheral sensitization defines a state in which primary afferent nociceptive neurons display enhanced responsiveness to external mechanical or thermal stimuli at the site of inflammation or injury [11].

- **Peripheral Sensitization:** Peripheral sensitization of the trigeminal nerve, and the blood vessels supplied by them, accounts for the throbbing pain. This stage of migraine is termed first-order neuron sensitization. Second-order neuron sensitization occurs when sensitization spreads to the second-order trigeminovascular neurons in the spinal trigeminal nucleus, causing scalp hypersensitivity or cutaneous allodynia. Third-order sensitization is the result of sensitization spreading to the thalamus, which causes extracephalic hypersensitivity [12].

Figure 1: Proposed pathophysiological mechanisms in the generation of migraine headache.

Current evidence indicates that cortical spreading depression (CSD) is the most probable primary event in trigeminovascular system (TGVS) activation in migraine with aura and, perhaps, also migraine without aura. Dysfunctional brainstem nuclei involved in the central control of pain might exert a permissive role by favouring central trigeminal hyper excitability. Abnormal cortical activity might lead to CSD when enhanced activation coincides with other triggering factors. The relationship between abnormal cortical activity and abnormal brainstem function remains hypothetical and unclear [13].

Resolution/postdrome phase

This phase is the final stage of attack; symptoms mimic first stage and lasting about hours or days to disappear the feeling of hangover or tiredness [14]. Nonheadache symptoms may start before the headache phase begins or during the premonitory period, the headache phase, or the postdrome. These symptoms involve brain activation of cortical and subcortical structures. Nonheadache symptoms may persist for 1 to 2 days after the headache has resolved in the postdrome or recovery phase [15].

A higher proportion experience a postdrome during which they may experience grumbling headache, a bruised feeling in the head, fatigue and nausea, and a continuing sensitivity to lights, noises, smells and movement [4]. Despite the fact that it can be equally or more disabling than the phases that precede it [16].

Classification of migraine

Due to the lack of pathognomonic markers for migraine, Co-occurrence of migraine subtypes and also the migraine and tension-type headache within the same individual and the lack of validity of the inclusion criteria and the boundaries between migraine and also for other headache subtypes, the classification of migraine has been delayed. There is an associated between the subtypes of migraine and its nature is defined by the International Headache Society Criteria and it is a Headache Classification Committee [17].

Classification of Migraine From The International Classification of Headache Disorders,3rd Edition (Beta Version)
1.1 Migraine without aura
1.2 Migraine with aura
➢ 1.2.1 Migraine with typical aura
☑ 1.2.1.1 Typical aura with headache
☑ 1.2.1.2 Typical aura without headache
➢ 1.2.2 Migraine with brainstem aura
➢ 1.2.3 Hemiplegic migraine
☑ 1.2.3.1 Familial hemiplegic migraine (FHM)
✓ 1.2.3.1.1 Familial hemiplegic migraine type 1(FHM1)
✓ 1.2.3.1.2 Familial hemiplegic migraine type 2(FHM2)
✓ 1.2.3.1.3 Familial hemiplegic migraine type 3(FHM3)
✓ 1.2.3.1.4 Familial hemiplegic migraine, other loci
☑ 1.2.3.2 Sporadic hemiplegic migraine (SHM)
➢ 1.2.4 Retinal migraine
1.3 Chronic migraine
1.4 Complications of migraine
➢ 1.4.1 Status migrainosus
➢ 1.4.2 Persistent aura without infarction
➢ 1.4.3 Migrainous infarction
➢ 1.4.4 Migraine aura-triggered seizure
1.5 Probable migraine
➢ 1.5.1 Probable migraine without aura
➢ 1.5.2 Probable migraine with aura
1.6 Episodic syndromes that may be associated with migraine
➢ 1.6.1 Recurrent gastrointestinal disturbance
☑ 1.6.1.1 Cyclical vomiting syndrome
☑ 1.6.1.2 Abdominal migraine
➢ 1.6.2 Benign paroxysmal vertigo
➢ 1.6.3 Benign paroxysmal torticollis

Table 2

Migraine without aura

Migraine without aura is a recurrent headache disorder which the attacks last anywhere from 4 to 72 hours. It has some common symptoms and most usual symptoms of the headache are unilateral location, a pulsating quality, which can range from mild, moderate and/or severe intensity and the intensity of headache may worsens by some routine physical activities and is associated with nausea photophobia and/or phonophobia [4].

Migraine with aura

Seen with Recurrent attacks, lasting within minutes and with unilateral fully reversible visual, sensory or other central nervous system symptoms, usually develop gradually and are followed by headache and associated migraine symptoms [4].

Aura symptoms
1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

Table 3

Before the headache starts, aura occurs which is described as a complex of neurological symptoms and the symptoms can be visual or sensory and may include blind spots, zig-zag lines, shimmering stars, changes or loss in vision and flashes of light [18].

Migraine with typical aura

Migraine with aura, in which aura consists of any of the fallowing symptoms alone or in combination they are of visual, sensory and/or speech/language symptoms, but no motor weakness, and it is characterized by gradual development, mix of both positive and negative features, duration of each symptom no longer than one hour and complete reversibility [4].

- **Typical aura with headache:** Migraine with typical aura in which aura accompanied by with or without migraine characteristics and fallowed within 60 minutes by headache [4].

- **Typical aura without headache:** The aura which is nei ther accompanied nor followed by headache of any sort is migraine with typical aura [4].

Migraine with brainstem aura

Migraine with aura symptoms that clearly originating from the brainstem but has no motor weakness [4].

Hemiplegic migraine

Migraine with aura which includes the motor weakness [4].

- Familial hemiplegic migraine (FHM): Migraine with aura including motor weakness, and at least one first- or sec ond-degree relative has migraine aura including motor weakness [4].
- Sporadic hemiplegic migraine (SHM): Migraine with aura which including the motor weakness and no first or second degree relative has the migraine aura including the motor weakness also [4].

Retinal migraine

This is the repeated attacks of monocular visual disturbance, which is including the scintillations, scotomata or blindness and are associated with migraine headache [4].

Chronic migraine

Headache occurring on 15 or more days/month for more than three months, which, on at least eight days/month, has the features of migraine headache [4].

Complications of migraine

1. **Status migrainosus:** A debilitating migraine attack last ing for more than 72 hours [4].
2. **Persistent aura without infarction:** This is the Aura symptoms which are persisting for one or more weeks without evidence of infarction on neuroimaging [4].
3. **Migrainous infarction:** This are One or more migraine aura symptoms occurring in association with an ischemic brain lesion in the appropriate territory demonstrated by neuroimaging, with onset during the course of a typical migraine with aura attack [4].
4. **Migraine aura-triggered seizure:** It is described as a seizure which is triggered by an attack of migraine with aura [4].

Probable migraine

Migraine-like attacks missing one of the features required to fulfil all criteria for a type or subtype of migraine coded above, and not fulfilling criteria for another headache disorder [4]

1. Probable migraine without aura
2. Probable migraine with aura

Episodic syndromes that may be associated with migraine

Recurrent gastrointestinal disturbance

Recurrent episodic attacks of abdominal pain and/or discomfort, nausea and/or vomiting, occurring infrequently, chronically or at predictable intervals, that may be associated with migraine [4].

- **Cyclic vomiting syndrome:** These are the recurrent episodic attacks with intense nausea and vomiting and these are usually stereotypical in individual and the episodes are with some predictable timing. The Attacks of this syndrome may be associated with pallor, lethargy etc and between this attack there is a complete resolution of symptoms [4].
- **Abdominal migraine:** This is an idiopathic disorder has recurrent attacks of moderate to severe midline abdominal pain, which is seen mainly in children and is associated with vasomotor symptoms, nausea and vomiting, which lasts from 2-72 hours and with normality between episodes and during these episodes headache does not occur [4].

Benign paroxysmal vertigo

It is a disorder which is characterized by recurrent brief attacks of vertigo, occurs without warning and resolving spontaneously, in otherwise healthy children [4].

Benign paroxysmal torticollis

These are the recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously and in infants and small children this condition occurs, with onset in the first year [4].

Diagnosing Migraine

The ICHD criteria for migraine and other primary headaches uniformly include “not attributed to another disorder” and recommend that secondary headache disorders suggested by the pa-

tient's history and/or physical and/or neurological examinations be excluded by "appropriate investigations." The presence of red, more so than yellow, flags increases the likelihood of a secondary cause of headache and should prompt further evaluation [19].

With no warning signs also, some cases with headaches begins and ends with sleep. In other cases, the headache may be preceded by a prodromal phase that includes extreme tiredness, depression, irritability, food cravings, a feeling of intense excitement or happiness, constipation, stiffness of neck, increased yawning, abnormal sensitivity to light, sound and also smell, and also just before and/or during the headache phase, an aura phase occurs which includes a variety of focal cortically mediated neurological symptoms [9]. Premonitory symptoms that warn of an impending migraine headache have been recognized for many years. Even after the headache has resolved, many patients are left with a postdrome that lingers for 1 to 2 days [20].

The group of typical symptoms which are experienced by the migraine sufferers is reflected in the ICHD criteria for the diagnosis of migraine [3].

In most patients, migraine can be diagnosed based on clinical criteria. When it cannot or when the patient's presentation suggests the possibility of a secondary cause of headache, the patient should be referred to a neurologist or other headache specialist. Neuroimaging is the best diagnostic tool for excluding most secondary headache disorders. CT imaging is preferred for ruling out acute haemorrhage, fracture, or paranasal sinus disease, while MRI is better if other conditions are suspected [19].

National institute of health and care excellence (nice) clinical guideline for migraine diagnosis

Headache feature	Migraine
Pain location (Headache pain can be felt in the head, face or neck)	Unilateral or bilateral
Pain quality	Pulsating (throbbing or banging in young people)
Pain intensity	Moderate or severe
Effect on activities	Aggravated by, or causes avoidance of, routine activities of daily living
Other symptoms	Unusual sensitivity to light and/or sound or nausea and/or vomiting
Duration	4-72 hours
Frequency	< 15 days per month (Episodic migraine).
	≥ 15 days per month for more than 3 months (Chronic migraine) [21].

Table 4

The ICHD diagnostic criteria for migraine

Diagnostic criteria for migraine without aura, from Headache Classification Committee of the International Headache Society (IHS),2018.
A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe pain intensity 4. Aggravation by or causing avoidance of routine 5. Physical activity (e.g. Walking or climbing stairs)
D. During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Table 5

Diagnostic criteria for migraine with aura, from Headache Classification Committee of the International Headache Society (IHS), 2018.
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura 1. Symptoms: 2. Visual 3. Sensory 4. Speech and/or language 5. Motor 6. Brainstem 7. Retinal
C. At least three of the following six characteristics: 1. At least one aura symptom spreads gradually over 5 minutes 2. Two or more aura symptoms occur in succession 3. Each individual aura symptom lasts 5-60 minutes 4. At least one aura symptom is unilateral 5. At least one aura symptom is positive 6. The aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis.

Table 6

Diagnostic criteria for chronic migraine, from Headache Classification Committee of the International Headache Society (IHS), 2018.
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 1.1 Migraine with- out aura and/or criteria B and C for 1.2 Migraine with aura
C. On 8 days/month for >3 months, fulfilling any of the following: 1. Criteria C and D for 1.1 Migraine without aura 2. Criteria B and C for 1.2 Migraine with aura 3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

Table 7

Diagnostic criteria for probable migraine, from Headache Classification Committee of the International Headache Society (IHS), 2018.
A. Attacks fulfilling all but one of criteria A-D for 1.1 Migraine without aura, or all but one of criteria A-C for 1.2 Migraine with aura
B. Not fulfilling ICHD-3 criteria for any other head- ache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

Table 8

Comorbidities with migraine

In some studies, it was said that in general population migraine occurs with some other illness also, and such illness occurrence are called as comorbidities.

The description or study on comorbidities of migraine is important, because it can help to understand the pathophysiology of migraine and also to improve the treatment strategies of migraine headache, so comorbidities should be described sufficiently [22].

In general, some headache disorders and particularly migraine have been linked with some comorbidities. The most commonly seen illnesses include hypertension, stroke, coronary heart disease, subclinical vascular brain lesions, diabetes mellitus, lumber and cervical pain, asthma, epilepsy, fibromyalgia, some psychiatric diseases like depression, anxiety, schizophrenia, panic disorder, suicidal ideations, bipolar disorder etc., are commonly seen illness [22,23].

Pharmacological treatment

The pharmacological treatment of migraine can be acute (abortive) or preventive, and patients with frequent severe headaches often require both approaches [25].

Acute treatment

Acute migraine attacks are treated with nonsteroidal anti-inflammatory drugs (NSAIDS), or triptans [26].

Acute migraine management nice guidelines
1. Combination therapy Non-Steroidal Anti Inflammatory Drug (NSAID) Or Paracetamol + Triptan + Antiemetic
2. Alternatively, (per patient request) a single agent (Triptan, NSAID Or Paracetamol) ± Antiemetic

Table 9

NSAID	DOSE
Naproxen	250 - 1000 mg
Diclofenac	50 - 75 mg (or 100 mg suppository)
Aspirin	600 - 1200 mg
Tolfenamic acid	200 mg
Paracetamol	1g
Aspirin	900 - 1200mg
Ibuprofen	400 - 800mg

Table 10

NSAIDS

By blocking cyclooxygenase nonsteroidal anti-inflammatory drugs (NSAIDs) decrease the synthesis of prostaglandins, which are involved in the pathophysiology of migraine headaches [27].

Pharmacologic treatment of migraine includes simple analgesics and NSAIDs for acute to moderate migraine attacks. NSAIDs inhibit the prostaglandin synthesis and prevent the neurologically mediated inflammation in trigeminovascular system. The absorption of NSAIDs and analgesics is increased and alleviate migraine related nausea and vomiting by the combination therapy with prokinetics such as Metoclopramide and domperidone. More than simple analgesics, over the counter combinations of acetaminophen, aspirin and caffeine was approved for treating migraine due to its efficacy in relieving the migraine pain and its associated symptoms [14].

Antiemetics

The nausea and vomiting that accompany the migraine headache are reduced or prevented by the adjunctive antiemetic therapy [30].

Drug class	Medication	Dose for migraine
Dopamine antagonists	Prochlorperazine	5 mg to 10 mg (Tablet) 25 mg (Suppository)
	Metoclopramide	10 mg (Tablet, oral suspension)
	Chlorpromazine	10 mg to 25 mg (Tablet)
	Domperidone	10mg up to three times a day (or 60 mg suppository)
Antihistamine	Promethazine	25 mg to 50 mg (Tablet) 25 mg (Suppository)
Serotonin (5-hydroxytryptamine 3) antagonist	Ondansetron	4 mg (Tablet) 8 mg (Orally disintegrating tablet).

Table 11

Triptans

Triptans, the 5-HT1B/1D receptor agonists, are having a major advance in the treatment of migraine headaches. Migraine patients have many beneficial effects with Triptans, as related to their multiple mechanisms of action at sites implicated in the pathophysiology of migraine. These mechanisms are mediated by 5-HT1B/1D receptors and include vasoconstriction of painfully dilated cerebral blood vessels, inhibition of nociceptive neurotransmission and inhibition of the release of vasoactive neuropeptides by trigeminal nerves. High affinity of the triptans for 5-HT1B/1D receptors and the favourable pharmacological properties contribute many beneficial effects of these drugs including rapid onset of action, fast and immediate relief from headache pain and associated symptoms and also low incidence of adverse effects [29].

Prophylactic/preventive treatment

Preventive treatment is used to reduce the frequency, duration or severity of attacks. Preventive treatment helps in reducing the migraine episodes and prevents the recurrent migraine attacks and result in reductions in the cost of health care [25].

Triptans	Starting dose	Target dose
Sumatriptan	50 mg-100 mg tablet	300 mg
	10 mg-20 mg nasal spray	40 mg
	25 mg suppository	-
	6 mg subcutaneous injection	12 mg
Zolmitriptan	2.5mg-5mg tablet	10 mg
	5 mg nasal spray	10 mg
Eletriptan	40 mg tablet	80 mg
Frovatriptan	2.5 mg tablet	5 mg
Rizatriptan	10 mg tablet	20 mg
Naratriptan	2.5 mg tablet	5 mg
Almotriptan	12.5 mg	25 mg

Table 12

Thus, migraine preventive treatment has to be considered in patients with:

a. Two or more attacks per month that significantly interf ere with the patient's daily routine activity and produce disability for 4 or more days per month;

b. An unsatisfactory or scarce response to acute therapy;

c. Contraindication to acute treatments and adverse effects (AE's) related to them;

d. The use of abortive medications more than twice per week;

e. Uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura or migrainous infarction [26].

Either Topiramate or a Beta blocker is tried first which are suggested by the current NICE guideline and if both the drugs are ineffective or contraindicated then gabapentin, acupuncture, botulinum toxin or riboflavin are considered [21].

Nonpharmacological treatment

Preventive migraine treatment also includes nonpharmacological therapy [24].

- **Cognitive Behavioural Therapy (CBT):** It is based on principle that anxiety and distress are aggravators of an evolving migraine headache.it is designed to help patient identify and modify maladaptive response that may trigger or aggravate a migraine headache [29].

Figure 2: *Algorithm for migraine prophylaxis [25].*

Drug class	Medication	Starting dose	Target dose
Beta blockers	Propranolol	10 mg three times daily	40 - 80 mg three times daily
	Metoprolol	25 mg twice daily	100 mg twice daily
	Atenolol	25 mg once daily	100 mg once daily
Serotonin antagonist	Pizotifen	0.5 mg OD, increase by 0.5 mg every 1 - 2 weeks	3 mg daily
Antidepressant	Tricyclic: Amitriptyline (alternatively nortriptyline)	10 mg	50 - 75 mg daily
	dosulepin	25 mg	7 5 - 100 mg
	SNRI: Duloxetine (alternatively venlafaxine)	30 mg	60 - 90 mg
Antiepileptic	Topiramate	100 mg	25 mg
	Sodium valproate	1000 mg	200 mg
Angiotensin based	Candesartan	4 mg OD	12 - 16 mg OD
	Lisinopril	10 mg OD	20 - 40 mg OD
Calcium channel blocker	Flunarizine	5 mg OD	5 mg for a month, then 10 mg
Nutraceutical	Riboflavin (vitamin B2)	400 mg daily	-
	Magnesium	600 MG DAILY	-
	CoQ10	100 MG TID	-
	Alpha Lipoic Acid	600 MG DAILY	-
Neuromuscular blocker	Onabotulinum toxin A(Botox)	200 U	-

Table 13

- **Complementary Treatments:** These include acupuncture or acupressure, massage, exercise and chiropractic, herbs etc., [14].
- **Yoga therapy:** Yoga, coupling physical exercise and breathing, meditation are the alternative form of mind body therapy and used to lower the symptoms of chronic pain, emotional stress, anxiety and depression [30].
- **Lifestyle Modifications:** Lifestyle impacts the severity and frequency of migraine can be understanding and useful for successful prevention of migraine.
- **Sleep:** Maintain consistent sleep patterns, including weekend and holidays
- **Exercise:** A routine of 20-40 minutes of aerobic exercise can relieve stress and maintain balance internal physiology.
- **Eating:** Have and maintain meals regularly and properly with good diet.
- **Reduce stress and increase posture:** Reduce stress with yoga, meditation and maintain posture that imparts migraine triggers [14].

Clinical trials

S. No	Drug	Author	Outcome and discussion	Phase of effectiveness	Conclusion
	Topiramate antiepileptic	Stephen D. Silberstein, MD; Walter Neto, MD; Jennifer Schmitt, MS; David Jacobs, MD	The primary efficacy assessment was a reduction in mean monthly migraine frequency across the 6-month treatment phase. Secondary end points were responder rate, time to onset of action, mean change in migraine days per month, and mean change in rescue medication days per month.		Topiramat, 100 or 200 mg/d, was effective as a preventive therapy for patients with migraine [1].
	Zolmitriptan triptans	G. Geraud A. Compagnon A. Rossi	Zolmitriptan was supplied as 2.5-mg oral tablets and the acetylsalicylic acid plus metoclopramide combination as oral sachets containing 900 mg of acetylsalicylic acid and 10 mg of metoclopramide. Blinding was maintained using a double-dummy technique. This randomised, double-blind trial was designed to compare zolmitriptan, a relatively new therapeutic option, with the oral combination therapy of acetylsalicylic acid plus metoclopramide in the acute oral treatment of migraine. Importantly, each drug was assessed in the treatment of 3 separate migraine attacks. This minimised the placebo effect, which can be considerable in migraine, and allowed evaluation of the consistency of the treatments efficacy. Each drug was used at recommended dosages and hence the results are applicable to the clinical setting. In analysing the results, we used the ITT population (all patients who took trial medication) to minimise any potential bias due to drop-outs.	zolmitriptan is consistently effective in the treatment of migraine with aura and migraine associated with menses. Indeed, zolmitriptan appeared to be more effective than acetylsalicylic acid plus metoclopramide in patients with migraine related to menses. Zolmitriptan was associated with a 2-hour headache response in a higher proportion of cases of migraine associated with menses compared with acetylsalicylic acid plus metoclopramide, both overall and at each attack.	zolmitriptan is consistently effective in the treatment of migraine with aura and migraine associated with menses In addition, the efficacy of zolmitriptan was unaffected by age, weight or gender [2].
	Donitriptan triptans	Gareth W. John, Michel Perez, Petrus J. Pauwels, Bruno Le Grand, Yvan Verscheure, and Francis C. Colpaert	Donitriptan is currently undergoing clinical evaluation for the acute treatment of migraine headache attacks. Based on the preclinical pharmacological characteristics of this compound, the following improvements over currently available triptans can reasonably be expected to include: a.) A larger percentage of migraineurs will be completely headache-free 2 h after treatment. b.) Consistency in headache response across the patient population studied can also be expected with donitriptan c.) A lower incidence of migraine recurrence. There are no expected disadvantages of donitriptan compared to the currently employed triptans, and systemic cardiovascular effects are expected to be similar.	A larger percentage (i.e., 40%) of migraineurs will be completely headache-free 2hr after treatment.	Donitriptan is a potent and selective 5-HT1B1D receptor agonist derived from 5-HT, which distinguishes itself from other triptans by exerting exceptionally high intrinsic activity (i.e., approaching that of the endogenous agonist 5-HT) at these receptors in vascular and neuronal models relevant to migraine [3]

Table 14

Conclusion

Migraine is a severe paroxysmal neurovascular disorder and considered a major cause of disability by the world health organization. The primary cause of a migraine attack is unknown but probably lies within the central nervous system. The classification of migraine has been impeded by the lack of pathognomonic markers for migraine but the nature of the association between subtypes of migraine defined by the International Headache Society (IHS) criteria. The typical constellation of symptoms experienced by migraine sufferers is reflected in the ICHD criteria for the diagnosis of migraine. The pharmacological treatment of migraine can be acute (abortive) or preventive, and patients with frequent severe headaches often require both approaches. Acute migraine attacks are treated with nonsteroidal anti-inflammatory drugs (NSAIDS), or triptans. Adjunctive antiemetic therapy is useful for combating the nausea and vomiting that accompany migraine headache. Preventive treatment is used to reduce the frequency, duration or severity of attacks includes beta blockers, serotonin antagonist, antidepressant, antiepileptic, and nonpharmacological therapy.

Authors Contribution

Poojitha Mamindla and Sharanya Mogilicherla both authors have contributed equally to this work.

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