RESEARCH PAPER

Unravelling the paradox of migraines: A comprehensive search of innovative therapeutic strategies

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Received: 25th Aug, 2026 | Revised: 1st Sep, 2026 | Accepted: 5th Sep, 2026 | Available Online: 7th Sep, 2026

ABSTRACT
Migraine, a prominent neurological condition, is estimated to have over one billion sufferers in the whole world. Recurrent moderate to severe headaches are its defining feature; these are often accompanied by phonophobia, photophobia and nausea and vomiting. This pathologic condition has a very significant impact on everyday life, productivity, and health in general. The review follows all the aspects of this disorder: prevalence, classification, mechanisms, symptoms, and present treatment options for migraine. This paper stresses that the key to its effective management and treatment lies in understanding the genetic predisposition, neurochemical imbalance, and common triggers of the migraine episode. In an attempt to address this, the paper considers different treatment modalities, ranging from acute to preventive pharmacological interventions, then non-pharmacological approaches—all of which are actually components of individualized treatment plans. It further underlines the role of continued research in enhancing migraine therapy and raising much-needed awareness of migraine as an important neurological disorder. This paper calls for a synthesis of current knowledge and gaps in understanding and treatment to continue advocating for improved care and support for those affected by this debilitating disorder and to encourage the integration of patient-centred care practices into the treatment of migraines.

Keywords: Migraine, Triggers, Trigemino-Vascular theory, Cognitive-behavioral therapy, Ditans, Acupuncture

How to cite this article: Wasu D, Chaudhari S., Unravelling the paradox of migraines: A comprehensive search of innovative therapeutic strategies. Int J Drug Deliv Technol. 2026;16(80s): 1722-1750; DOI: 10.25258/ijddt.16.80s.213

1. Introduction

Migraine is a neurological disorder which occurs with recurrent episodes of mild to severe headaches based on cumulative body functioning of a particular individual [1]. Such headaches are usually unilateral and can be associated with or without an aura, which are accompanied by the symptoms of migraine [2]. These warning signs may include flashes of light, blind spots in vision, tingling in arms or legs that may last from 5 to 60 minutes prior to onset of pain mimicking stroke-like symptoms. Migraines often cause nausea, vomiting,

sensitivity to light and sound which can last several hours to even days significantly interfering with an individual's lifestyle [3].Victims of migraine may see a significant loss in their quality of life since they can be very disruptive to daily routines. The unpredictable nature of migraine may generate a sense of instability and distress, adding to the overall burden of aforementioned disorder. An individual dealing with the pain is in a state of vulnerability, anxiety and depression, thus, negatively impacting on one's quality of life. Recent data portrayed that approximately 1 billion people suffer from migraine headaches in the world [4,5]. The pathophysiology of migraine remains debatable, as do absolute treatment options. Evolution of three predominant migraine pathophysiological hypotheses, are documented namely vascular, neuronal, and trigeminovascular theories. Considering the "vascular theory", it leads to extra-cerebral or cerebral dysfunction. The second, that is "neuronal theory" hypothesizes that migraine pathophysiology incepts with Cortical Spreading Depression (CSD). The third, "trigeminovascular theory" speculates the origin of migraine via inflammation at the trigeminal nerves and vessels surrounding these within trigeminal ganglion cells. Trigeminovascular theory is the most commonly accepted and corroborated etiological concept of migraine. The sensory fibres of the external and internal carotid arteries, which constitute a part of numerous nerve receptors may play an undefined but key role in manifesting pain in the head and its connective cutaneous allodynia during a migraine attack [6].

Migraine awareness is essential for its distinctive management and treatment plan. An integrated blue print is required which involves medication, changes in lifestyle and a fraction of behavioural therapy. Early diagnosis aids individuals to cooperate with health professionals to build personalized plans of treatment targeted at lowering the frequency and severity associated with episodes of migraine. A sound apprehension of migraine is vital for managing it on a personal level. It also has relevance for public health policy, workplace accommodations and research priorities. Acknowledging the enormous burden associated with patients experiencing migraines, scientists must avail a combination of novel therapeutic and non-therapeutic approaches to mitigate the symptoms of migraine [7,8] (Figure 1). So, in order to combat a disorder like migraine, this article will delve deeper on pathophysiology, causes, symptoms and diverse types of treatments that are currently available for its prevention, along with the future aspects to cope with this critical disorder.

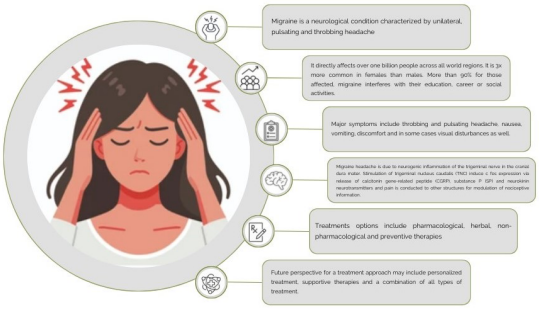

Fig 1: Aspects of Migraine

2. Prevalence of Migraine

Migraine is one of the major health issues round the globe which needs to be pondered as it is estimated to affect nearly 12% of the overall population. This neurological disorder has been ranked second in the global burden of diseases that implied its prevalence across different regions. Cost of healthcare differs based on the

geographical alterations worldwide. Literature indicated that the occurrence differs by demographics, namely gender and age [9]. There is a significantly large effect of gender on the frequency of migraine, a condition largely observed in females. Approximately 18% of women population suffer from migraine while, for men only 6% are sufferers. This difference is believed to be greatly influenced by hormonal factors that explain the increased prevalence in women during their reproductive years. Taking into account the factor of age, incidence of migraine is discerned amid 25 to 55 years of age, a time period viewed as peak productive years, therefore increasing its societal and economic impact [10].

Only in the United States, based on the variables assessed, it is reported that a tremendous annual estimate of about on $17 to $36 billion annually is spent on healthcare in the management of migraine. This is applied to both in the form of direct costs, including the medical expenditure for visiting healthcare providers, diagnostic tests, medications and indirect costs due to reduction in work efficiency [11]. Besides the economic burden, migraine is also a cause of major impairment to the standard of living. The chronic and episodic nature of this disorder, added to the possibility of severe pain and associated symptoms which gravely limit the possibility for the subjects to participate in daily activities, to maintain social relationships, and to fulfill work and family responsibilities [12].

The aspect of epidemiology in case of migraine underscores as a health problem with huge disparities in sex and age distribution. The burden of this disorder deeply influences the socioeconomic aspects via expenditure on healthcare, decrease in the productivity of work and the level of comfort of the affected individual. This burden of migraine needs to be managed comprehensively, from focused research to effective supervision towards the implementation constructive public health policies [13].

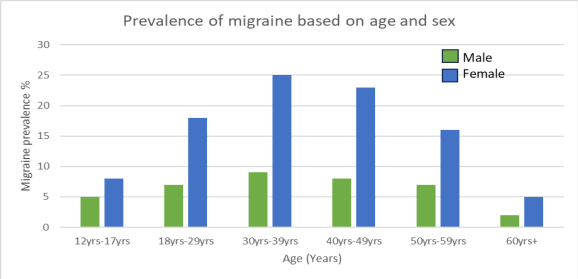

Fig 2: Prevalence of Migraine based on Age and Sex

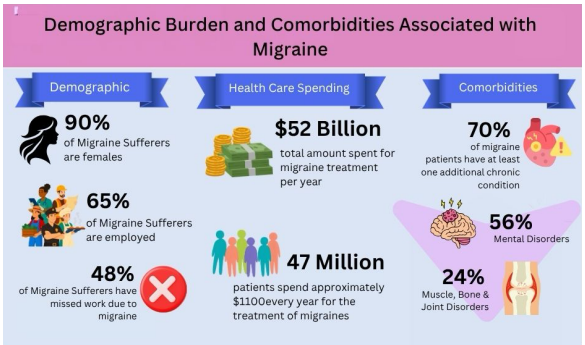

Fig 3: Migraine Demographics

3. Types of Migraine

Migraine a broader disorder, which has a spectrum of subtypes displaying different symptoms, diagnostic criteria and indications for its management. The common subtypes of migraine are migraine without aura, migraine with aura, chronic migraine, vestibular migraine and hemiplegic migraine. It is exceptionally critical to have insights of these subtypes for proper diagnosis and application of appropriate treatment approaches [14,15].

3.1. Migraine without aura

This is the most regular subtype and includes about 70-90% of all migraine cases that is characterized by episodes of headache, which last from 4 to 72 hours featuring unilateral, pulsating pain of moderate to severe intensity. The headache

episodes may be accompanied by nausea, vomiting and sensitivity to light and sound. In this subtype, there are no neurological symptom like aura preceding the headache unlike in other forms [16–18].

3.2.Migraine with Aura

This type includes about 20-30% of population which is impacted by migraine consisting of neurological symptoms, one or more, which precede or accompany the headache also called aura. Most auras are visual disturbances like flashing lights, zigzag lines and short-term vision loss. Less prevalent aura includes sensory, speech and motor disturbances. Gradually, each aura symptom develops over several minutes and may last for up to an hour [19,20].

3.3.Chronic Migraine

This subgroup is diagnosed when a subject encounters 15 or more headaches per month with a minimum criterion of 8 days associated with migraine for more than three months. The occurrence of this subtype of migraine in general population is about 1-2%. It stands at the extreme end of the spectrum, showcasing the disorder in its most severe and frequent form, usually producing substantial disability and greater burden of disorder [21,22].

3.4.Vestibular Migraine

The diagnosis of vestibular migraine directs a complaint of discombobulation, vertigo and balance problems associated with symptoms of migraine. These vestibular symptoms can occur in the time frame of the headache phase. Diagnosis is thus based upon patient history and exclusion of other causes for vertigo. The estimated occurrence for vestibular migraine is about 1% of the population, although it is probably under diagnosed [23–25].

3.5.Hemiplegic Migraine

This is rather a rare class of the disorder that implicates temporary paralysis or weakness on one side of the body as a phase of aura. Other aura symptoms such as vision troubles, improper speaking and sensory disturbances, can be observed in hemiplegic migraine. This subclass can further be categorized into familial and sporadic hemiplegic migraine based on the presence or absence of family history. The actual prevalence of hemiplegic migraine, has been estimated to be less than 0.01% in the population [26,27].

These subtypes of migraine vary in frequency and occurrence in the population, showing a broad spectrum of manifestations for this heterogeneous condition. Thus, a great understanding of the patient history and cautious assessment of symptoms with adherence to established diagnostic criteria, such as the International Classification of Headache Disorders, are usually key elements of an accurate diagnosis. To design treatment strategies that will yield better management and outcomes, understanding the characteristic features of the different classes of migraine is necessary [28].

Table 1: Summary of types and symptoms of migraine

Type of Migraine	Symptoms	Population Affected	Other Information
Migraine without Aura	Unilateral pulsating headache lasting 4 to 72 hours. Nausea, vomiting, photophobia, and phonophobia	70-90% of migraine sufferers	Does not include neurological symptoms (aura)
Migraine with Aura	Visual disturbances (flashing lights, zigzag lines) Sensory, speech, or motor disturbances during aura	20-30% of individuals with migraine	Aura precedes or accompanies the headache
Chronic Migraine	≥15 headache days/month for >3 months, ≥8 days meeting migraine criteria	1-2% of the general population	More severe and frequent, significant disability
Vestibular Migraine	Dizziness, vertigo, balance problems. Associated with migraine headache symptoms	~1% of the population	Often underdiagnosed
Hemiplegic Migraine	Temporary paralysis or weakness on one side of the body during aura. Visual disturbances, difficulty speaking, sensory changes	<0.01% of the population	Categorized into familial and sporadic hemiplegic migraine

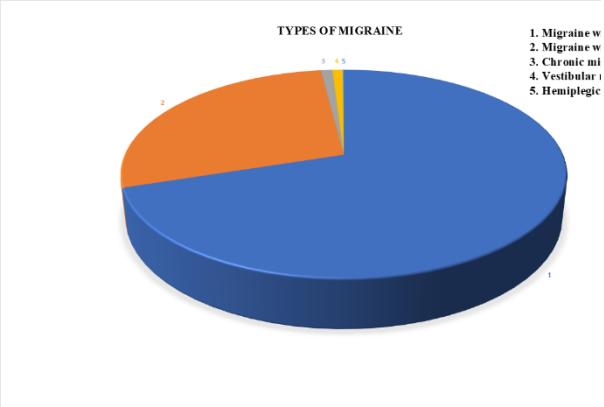

Fig 4: Graphical representation of types of Migraine

4. Causes of Migraines

The etiology of migraine is diversified, including genetic predisposition, neurochemical modulation and an assortment of environmental triggers. This complexity of interface presents a challenge in effectively managing and averting the disorder. All of these components interrelate in a way that there is crucial needs to understand in developing interferences which are aimed at helping patients reduce the reoccurrence and intensity of migraine attacks [29].

4.1. Genetic Factors and Familial Predisposition

There is a sizable hereditary component linked to migraine, evidenced by plenty of studies indicating prevalence among subjects with a family history of the disorder. For instance, a person with a first-degree relative having migraine has a substantially increased risk for the condition. Recent scientific data revealed that genetic factors have been associated with migraine, especially for genes involved in familial hemiplegic migraine, thus indicating an inheritable component for its transmission. However, the pattern of inheritance is complex and polygenic, involving multiple genes and environmental elements. This factor definitely speaks of the heterogeneity of migraine and the necessity of tailoring approaches in therapy and management [30–32].

4.2.Neurochemical Imbalances

The release of neurochemicals, mainly serotonin and its fluctuating levels is the root cause for the pathogenesis of migraine. Thus, considering these changes, along with other neurotransmitter imbalances, it has been postulated that they may play a paramount role in the initiation of a migraine attack. Engagement of this neurochemical is further supported by the fact that some anti-migraine drugs are effective because they alter the serotonin levels. The release of neuropeptides, like calcitonin gene-related peptide, leads to inflammation and vasodilation in the brain, which amplifies the pain of a migraine headache. Thus, the pharmacological mechanism of migraine deals with a complex interplay of neurochemicals, which dictates therapeutic approaches toward the treatment of such a disorder [33–35].

5. Common Triggers

The migraine attack can be instigated by a very broad range of factors that further underlines the establishment and management of individually specific triggers [36]. Triggers associated with migraine include:

5.1. Stress

Commonly recognized trigger for migraine is stress, that when experienced implicates to our body undergoing physiological changes which includes the release of stress hormones like cortisol. These hormonal fluctuations can lead to blood vessel constriction and subsequent dilation, which may trigger migraines in susceptible individuals. Preventive strategies such as relaxation techniques, mindfulness and

stress management can help reduce the impact of stress-related migraines [37].

5.2. Hormonal Changes

Hormonal fluctuations play a significant role in migraine occurrence, especially in women. Scenarios in which women particularly experience migraine attacks are menstrual cycles (drop in estrogen levels), pregnancy and menopause, that are connected with alterations in the levels of hormone thereby triggering migraine [38].

5.3.Dietary Factors

Certain foods and beverages are notorious for triggering migraines namely:

5.3.1. Aged Cheese: Contains tyramine, which can provoke headaches.

5.3.2. Processed Meats: Nitrites and nitrates in cured meats may contribute to migraines.

5.3.3. Chocolate: Major constituents like phenylethylamine and caffeine, both are potential triggers for a migraine attack.

5.3.4. Caffeine: While some find it helpful, excessive caffeine intake can lead to rebound headaches [39].

5.4. Environmental Factors

Prominent environmental factors which trigger migraine are majorly sensory stimuli which include:

5.4.1. Bright Lights: Intense light, especially fluorescent or flickering light, can be problematic.

5.4.2. Loud Sounds: Noise sensitivity is common during migraines.

5.4.3. Strong Odors: Perfumes, cleaning products, or other strong smells may trigger attacks.

5.4.4. Weather Changes: Barometric pressure shifts can affect blood vessels and trigger migraines [40].

5.5.Sleep changes

Sleep disturbances can impact migraines that aggravates based on the stages of sleep.

5.5.1. Missed Sleep: Lack of sleep or irregular sleep patterns can trigger attacks.

5.5.2. Excessive Sleep: Oversleeping can also be problematic.

5.5.3. Jet Lag: Rapid time zone changes disrupt our body's internal clock and may lead to migraines [41].

5.6. Physical factors

Intense physical exertion, including sexual activity, can provoke migraines. The exact mechanism is not completely known, but sudden changes in blood flow and muscle tension likely play a role [42].

5.7. Medications

Some medications can worsen migraines like oral contraceptives (hormonal birth control can affect migraine frequency), vasodilators like Nitroglycerin dilate blood vessels and may trigger headaches [43].

The causes of a migraine are various, ranging from genetic predispositions to neurochemical imbalance, including a variety of possible triggering factors. This makes it very complex and thus must be addressed in a holistic approach to treatment and management, a consideration that covers from genetic counselling to lifestyle modifications and when necessary, pharmacological interventions that address the individual needs of every person [44].

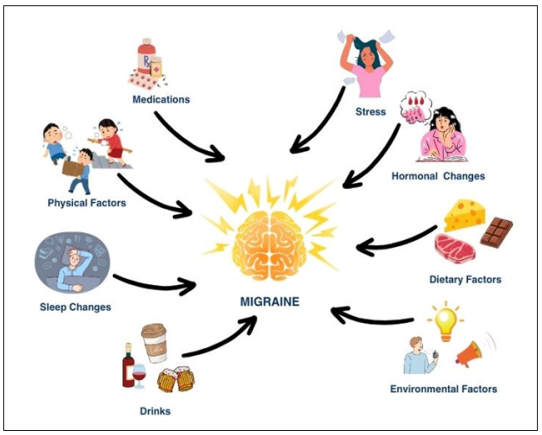

Fig 5: Triggers manifesting migraine

6. Symptoms of Migraines

Migraine is a condition, exhibiting a set of symptoms which may shift significantly with respect to type and severity from one individual to another. Various signs indicating migraine are divulged as hallmark, additional and aura indicators [15].

6.1. Hallmark symptoms

The most prominent symptom of migraine would have to be the throbbing or pulsating headache, which usually resides on one side of the head but could appear in both. The pain is usually of moderate to severe intensity and is often intensified by physical activity. Coupled with the headache, nausea and vomiting are ubiquitous and add to the overall discomfort and feeling of debilitation in due course of an attack [45].

6.2. Additional Symptoms

Apart from the major symptoms, patients who have a migraine frequently report an escalated sensitivity to environmental stimuli. Photophobia that is sensitivity to light and phonophobia which is fear of sound are prevailing symptoms [46]. These susceptibilities could elevate the pain and result in avoidance behaviors where patients retreat to dark and quiet rooms. Other common symptoms include osmophobia which is seldom discussed but equally distressing and dizziness or vertigo, which further adds to difficulty in management of daily activities [47].

6.3. Aura Symptoms

About 20-30% of patients with migraine do experience aura, which is an assemblage of neurological symptoms that usually rule over the headache phase of migraine but may also incept at the same time or after the headache [48]. The most common aura symptoms are visual disturbances which include flickering of lights, zigzag lines or temporary loss of vision. Auras may also take the form of sensory alterations for example, tingling or numbness, typically on one side of the body or, less often, as motor weakness. These symptoms usually soar gradually, evolve over several minutes and last less than an hour. In many cases, aura adds to the complexity of migraine and can even be alarming or leading to anxiety in those individuals which are not familiar with this phenomenon [18].

Knowing the degree and character of migraine symptoms is crucial to both the sufferer and health professionals. It guides in the identification of the migraine attacks and in opting for treatment choices; it helps in the formulation of strategies aimed at mitigating and coping with the symptoms [49]. Management as well as preventive measures have to be tailored according to an individual, considering his or her particular symptoms and triggers. These hallmark symptoms, added to additional symptoms and aura occurring in some, complicate this disorder and make an accurate diagnosis and effective management difficult [50].

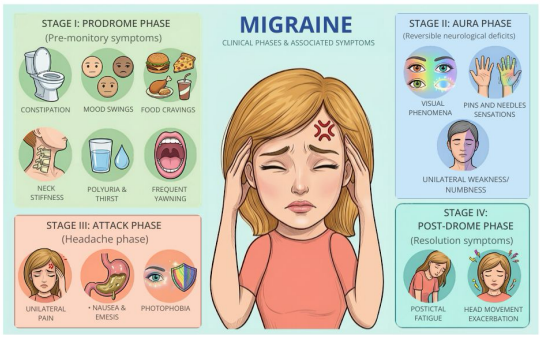

Fig 6: Various symptoms of Migraine according to different phases

7. Stages of Migraine

Migraine symptoms can occur in four major stages namely prodrome, aura, attack and post-drome. While these stages provide an outline for analyzing migraine attacks, it's crucial to recognize that not everyone experiences all of them. Some individuals may skip certain phases altogether, while others consistently experience the entire sequence. Migraines are highly person specific and the presence and intensity of each stage can vary individually [51].

7.1. Prodrome

Patient may or may not experience some vague changes for one or two days before an attack, these changes are known to act as warnings for the approach of a migraine. They include constipation, mood changes, food cravings, neck stiffness, increased urination and frequent yawning [52].

7.2.Aura

An aura is a reversible symptom of the nervous system. Some people may experience an aura before or during a migraine. They are usually visionary, but can also be of another type of disturbance. Each symptom typically initiates slowly, builds up during the course of several minutes, and lasts for 20-60 minutes [53].

7.3. Attack

Attack is connected via pain that is usually on one side of the head characterized bypulsating or throbbing ache. Predominantly attack in migraine may also include sensitivity to light, sound, smell and touch leading to ultimately nausea and vomiting [54].

7.4. Autonomic instability

In this stage of migraine, due to the dysfunctioning of autonomic nervous system it leads to a negative impact on various bodily functions like blood pressure and digestion [55].

7.5.Post-drome

Patient suffering from migraine can feel tired, dazed and washed out for up to a day after a migraine attack. Some people feel euphoric, sudden head movement may lead to reoccurrence of back pain [56].

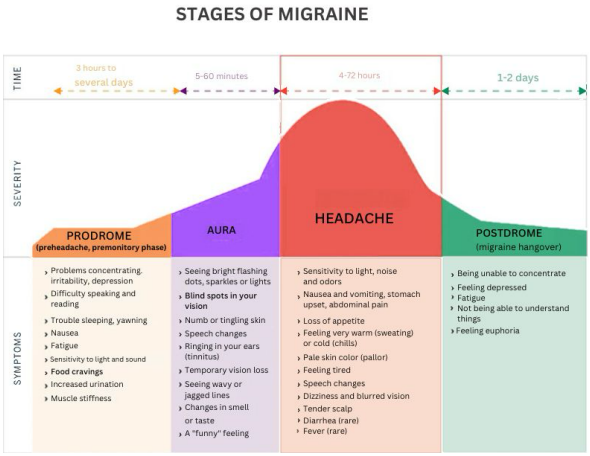

Fig 7: Stages of Migraine

8. Pathophysiology

Migraines are part of neurovascular pain conditions with altered central neuronal processing [57,58]. While the exact mechanisms behind multifactorial and complex nature of migraine pathophysiology's have not been fully understood, it is believed to involve the following key mechanisms:

In the 1940s, "vascular theory" documented changes in the structure of brain blood vessels which led to migraine [59]. Soon after, an association between migraine aura and CSD in the cortex of the brain was considered. In 1981, Olesen and coworkers published the "neuronal theory" where

CSD, a prime cause of migraine, was situated in the cortex of the brain. The difficulty in the neuronal theory was to find a place for migraines without aura [60]. Later, Moskowitz and others described the "trigemino-vascular theory" which activates trigeminal nerves and vessels which is followed by inflammation as a trigger of migraine. Numerous neurochemicals such as serotonin, calcitonin gene-related peptide, substance P, nitric oxide and dopamine have been recognized to be involved in migraine pathophysiology. The recent development of imaging techniques with positron emission tomography and fMRI has found abnormal hypothalamic activity even before the headache phase of the migraine. Another neurochemical like PACAP38, which originated from the hypothalamus, has been linked to migraine attacks. Understanding these neural mechanisms along with advanced imaging techniques gave meaning to the earlier hypotheses about migraine and actually revealed the pathophysiology of the migraine [61].

8.1. Vascular Theory

The "vascular theory" of migraine, proposed by Wolff and his colleagues, postulated that aura emerges due to the constriction of blood vessels in the brain, followed by excessive dilation, which in turn irritates the pain sensitive nerves surrounding the vessels, leading to severe headache [62]. According to this theory, migraine attacks are due to unwanted reactions to stimuli or substances that influence blood vessels inside and outside the cerebral matter. Serotonin is probably a vital component in the vascular theory of migraine that exerts vasoconstriction and is stored, in high levels in the platelets of blood [63]. After being broken down, the platelets release 5HT into the blood stream by stimulation from stress or other triggers to act on 5HT receptors in blood vessel endothelial cells and cause vasoconstriction. This aspect is believed to be equivalent for the onset of migraine aura, particularly in the occipital lobe. The subsequent depletion of released 5HT leads to vasodilatation and a migraine attack [64].

8.2.Neuronal Theory

Lashley (1941) described his own migraine aura and calculated an approximate speed for the visual aura in the visual cortex at the distal region of the brain. In 1944, Leao stated a phenomenon in rabbits whereby there is temporary suppression of brain activity, propagating sequentially across the brain surface in a radially spreading fashion following stimulation, which he termed cortical-spreading depression (CSD) [65]. Milner (1958) proposed that the CSD velocity was analogous to the velocity of migraine visual aura spread, therefore suggesting a potential interrelation between CSD and migraine aura [66]. Olesen gauged local brain blood flow fluctuations in patients with migraine and auras. Lauritzen put forth the "neuronal theory" that portrays changes in nerve cell activity, and not just temporary blood vessel constriction which play a primary role in migraine pathophysiology. Hadjikhani reported a decrease of blood flow detected by fMRI during migraine attacks, thus supporting changes of brain activity in migraine. It has been shown by various researches that the migraine attacks are foreshadowed by a phase of decreased blood flow before the dilation of blood vessels therefore, migraine pathophysiology is put forth as a result of the complex interplay of factors [67].

8.3. Trigemino-vascular Theory

The trigemino-vascular theory suggested that the stimulation of nerve endings of the

trigeminal nerve surrounding the blood vessels in the cerebral cortex leads to migraine attacks [68]. Excitation of these nerve endings results in the release of CGRP, SP, neurokinin Aand other factors, causing vasodilatation and elevated permeability in blood vessels. This dilatation of blood vessels might result in plasma protein leakage, degranulation of surrounding cells, and a wider vascular expansion with neurogenic inflammation. The alarming pain signals move from the trigeminal ganglion to the trigeminal nucleus in the brainstem and then project to higher brain centers that contributes to the headache phase of a migraine attack [69]. Theoretically, symptoms such as nausea and vomiting during a migraine attack might be related to projections from the trigeminal nucleus to various other nerve centres in the brainstem. While such a theory may fit relatively well with clinical symptoms, it does not explain the trigger of the migraine or the premonitory phase. More specifically, how cortical spreading depression relates to changes in brain blood flow during attacks and neurogenic inflammation remains unknown [70].

According to a series of recent studies, it is observed that changes in the brain might start even before the time of the flashing lights and blind spots, the typical visual disturbance that marks the aura phase. These very early changes within the brain have been hypothesized to begin even at an earlier phase called the premonitory phase, which precedes the aura phase and may themselves have a role in triggering a migraine attack [71]. The predominant premonitory symptoms are frequent yawning, fatigue, diminished concentration, neck and shoulder stiffness, and feelings of melancholy. Characteristically, these symptoms are very broad and diverse therefore, it is critical to anticipate the onset of a migraine attack. Understanding of these initial changes in the brain and associated symptoms occurring during the premonitory phase is of importance for the development of initial insights of the mechanisms underlying migraine and may also have potential significance for the development of more effective treatment strategies [72].

9. Approaches for the treatment of migraine

Treatment choices of migraine encompass acute management, preventive strategies, and non-pharmacological therapies. Acute therapy relieves symptoms during attacks and even reduce the frequency or severity of future episodes. Treatment strategies for migraine may vary depending on frequency of attacks, severity of symptomsor patient preferences [73,74].

9.1. Acute Treatment Options

The patients with a history of migraine headaches require an individual acute treatment plan based on their prior medical history and characteristics of migraines. Important factors that should be taken into account include intensity of the headache, time taken to reach peak intensity and severity of concomitant symptoms [75]. Choice of treatment strategy, will completely depend upon patients' overall medical record. Most migraine patients are not satisfied with the current ongoing medication and accessibility of drugs also vary in particular countries [74].

9.1.1. Stratification of acute treatment for migraine

Acute treatment strategies are bifurcated into three different types namely stratified care, stepped care across migraine and stepped care within migraine [73].

9.1.1.1. Stratified Care

An initial selection of acute medication is based on the severity of migraine related disability where the degree of disability decides the dose required for the treatment. For instance, in a case where migraines are dominant over daily life, strong medications may be prescribed [76].

9.1.1.2. Stepped Care Across Migraine Attacks

A staircase approach involving the slow escalation of treatment alternatives can be employed. The step taken may includea simple analgesic, usually acetaminophen or aspirin. Proceeding ahead, the patient will continue the same drug for three consecutive attacks. If there has been an inadequate relief at the previous stage, the patient will be offered an antimigraine agent for subsequent attacks, usually a triptan [77].

9.1.1.3. Stepped Care within Migraine Attacks

In this stage of migraine, simple analgesics are taken at the time of an attack, if pain persists a patient should switch to an antimigraine medication within the same attack [78].

9.1.1.3.1. Simple Analgesics

Paracetamol, NSAIDs like ibuprofen, aspirin, and diclofenac, are utilized for migraine headaches, but paracetamol is not regarded as the drug of first choice. Ibuprofen has been used to provide a pain-free response within 2 hours of treatment in 26% of the patients with moderate-to-severe migraine attacks. This stated that about a quarter of those treated using ibuprofen were relieved from pain within the 2-hour time frame. Likewise, aspirin when administered during the attack, 24% of individuals were pain-free after 2 hours. Therefore, aspirin had a positive response toward pain alleviation during a migraine attack, similar to ibuprofen. These aforementioned results demonstrated the efficacy of ibuprofen and aspirin in pain mitigation due to a migraine attack within a relatively short period; hence, establishing the role of these drugs in an acute attack of a migraine [79,80].

9.1.1.3.2. Triptans

These class of drugs available in several formulations, of which Sumatriptan is the most widely used and prescribed. They are effective for attacks of moderate to severe intensity of headache, particularly if taken early in the headache phase. It was observed that post oral administration of Sumatriptan, 32% of patients were free of pain versus 11% with placebo. Subcutaneous injection ofSumatriptan produces pain relief in 59% of population. Sumatriptan combined with Naproxen is effective. Recurrence rates vary from 17-40%, influenced by drug half-life and receptor potency. Cautioning is advised in patients with cardiovascular history due to triptans' vasoconstrictor effects [81–83].

9.1.1.3.3. Gepants

In the 1990s triptans, the serotonin 5-HT1B/1D receptor agonistsemerged as acute therapy for migraines. However, the vasoconstrictor effects observed in patients with cardiovascular and cerebrovascular diseases gave rise to concerns about their widespread application. During a migraine attack, it was found that there were high levels of CGRP. Provocation studies demonstrated that exogenous CGRP could trigger migraine-like symptoms, and these were abolished by triptans. These findings gave way to the development of Gepants [84,85].

Ubrogepant showed efficacy following completion of two positive phase 3 studies (ACHIEVE I and II). In the single-blind, placebo-controlled ACHIEVE I study, 1327 patients were randomized to placebo

and Ubrogepant 50 mg or 100 mg. Both dosages hit endpoints for pain freedom at 2 hours and for reducing bothersome symptoms compared with placebo. ACHIEVE II studied 1355 patients, randomizing lower doses of 25 and 50 mg where the pain relief results turned out statistically significant. The 50 mg dose also demonstrated relief from bothersome symptoms for 2 hours [86,87].

Ubrogepant has recently been approved by the FDA for the acute treatment of migraine in adults with and without aura. In a recent phase 3 trial published in July 2019, the efficacy of Rimegepant in treating acute migraines was assessed against placebos. The results were promising, with 19.6% of patients receiving Rimegepant who achieved pain freedom at 2 hours, as compared to 12.0% in those receiving placebo. For freedom from the most bothersome symptoms, 37.6% was obtained with Rimegepant versus 25.2% obtained with the placebo. Safety and tolerability were very much like the placebo. Common adverse events included nausea and urinary tract infection. Rimegepant is under investigation in a phase 2 trial for the prevention of migraine. If efficacy is proven, it will be the first Gepant clinically established as effective for both acute treatment of migraine and migraine prevention [88].

Atogepant is a novel oral CGRP receptor antagonist specifically developed to prevent the onset of migraine. It has been presented at the 2018 American Academy of Neurology and American Headache Society Scientific Meeting; promising results were shared for its studies in patients with episodic migraine. In a study of 834 subjects, placebo-controlled, across five single doses of atogepant, patients treated with atogepant showed a 4-day average reduction in migraine per month. The results have not yet been fully published, and a phase 3 trial for its use in preventing chronic migraine is still ongoing [89,90].

9.1.1.3.4. Ditans

The clinical trial data of Lasmiditan (first generationditan), revealed that in the phase III study patients with moderate to severe attacks of migraine, achievedpain freedom at 2 hours with 200 mg Lasmiditan by 32% and with 100 mg by 28%, compared to 15% with placebo; the results were replicated in a second cycle of phase III study. However, Lasmiditan is linked with temporary driving impairment and a lack of ability to self-assess the level of impairment. In patients where NSAIDs and triptans are ineffective or contraindicated, Lasmiditan will remain a drug of choice [91].

9.1.1.3.5. Antiemetics

Antiemetic's should be provided as adjunctive management to patients with refractory nausea or emesis as part of their attacks. Chlorpromazine administered via intramuscular and intravenous route significantly increased analgesic effect at 2 hours and 1 day respectively (low strength of evidence) [92]. Prochlorperazine in the form of oral and rectal formulations, and Droperidol as intramuscular administration, showed an improvement in pain relief at 2 hours with a low strength of evidence [93]. Intravenous Metoclopramide and intravenous Haloperidol were associated with improved pain relief at 2 hours with low strength of evidence. However, all three of the aforementioned drugs haloperidol, chlorpromazine and prochlorperazine showed a noteworthy increase in the risk of adverse events [94].

9.2. Herbal Treatment Options

There is an active interest in exploring novel treatments for migraine by

individuals suffering from the condition due to side effects and limitations of conventional pharmacological therapies. This interest has impelled clinicians and researchers to continue exploring plant-based therapies for the management of migraine and possible mechanisms of action. The relevance of these alternative treatments are rapidly growing as scientists seek novel approaches to the management of this disabling disorder [95]. Some of the herbs employed in the management of migraine are elaborated below:

9.2.1. Turmeric (Curcuma longa)

Curcumin is extracted from the rhizomes of turmeric and exhibits varied health benefits, such as potent antioxidant and anti-inflammatory activities. Studies have shown that curcumin, when combined with CoQ10 or Omega-3, decrease the occurrence and intensity of a migraine [96]. Animal studies suggested that it reduces the intensity of the disorder due to its antioxidant and anti-inflammatory effects [97]. Curcumin is usually safe in low doses, with minor side effects, but it revealed drug-drug interactions. Need of extensive research in using curcumin to treat migraines individually or in combinations with other herbs is essential.

9.2.2. Coriander (Coriandrum sativum)

Coriander is native to the Mediterranean region and is an herb that has been a choice in cooking and folk medicine against different gastrointestinal complaints. Seeds of coriander contain various essential oils, majorly linalool and petroselinic acid which provide their distinct health benefits that include antimicrobial and anti-inflammatory properties [98]. One study stated that coriander syrup reduced the degree and frequency of migraines, although further research is needed due to the small sample size. Portraying analgesic and anti-inflammatory potentials, coriander may be one of the options for the treatment of migraine. However, people with low blood sugar or pressure levels should be cautious while its consumption [99]. Overall, coriander does exhibit promisingactivity for the treatment of migraine, based on its safety profile and other beneficial constituents.

9.2.3. Peppermint (Mentha piperita)

Menthol is a primary potent ingredient of peppermint and spearmint, that produces a cooling sensation on application over the skin and mucosal surfaces by developing action upon the sensory nerves and smooth muscle fibres [100]. Considering the history, menthol is used as a local anaesthetic, counter-irritant and non-opioid analgesic. Studies have reported the role of menthol in reducing pain, nausea, light and sound sensitivity. Peppermint oil also decreases the intensity and duration of the headache in migraine [101]. Menthol can act via receptor (**TRPM8**) action, blockage of nerve signals, and anti-inflammatory actions [102]. Safety profile of menthol divulged that it was generally well tolerated, though some burning sensation and increase in lacrimation was reported. Further studies are needed to ascertain the effectiveness and safety of menthol for migraines [103]. Menthol would therefore, emerged to have some potential in migraine management by its cooling, analgesia, and anti-inflammatory properties.

9.2.4. Chamomile (Matricaria chamomilla L)

Chamomile, scientifically known as *Matricaria chamomilla L*, is an herb that is a member the Asteraceae family. It is naturally found in southern and eastern Europe. It possesses prominent antibacterial, anti-inflammatory, antispasmodic, antioxidant and anxiolytic

activities. Traditionally, it was used in gastrointestinal disorders, intermittent feverand sleeplessness. Among its major phytoconstituents, the active compounds are sesquiterpenes, coumarins, flavonoids, and polyacetylenes [104]. Blue essential oil obtained from flowers of Chamomile that chiefly consists of terpenes like bisabolol, farnesene, chamazulene, with flavonoids, including apigenin, quercetin, patuletin, and luteolin [105]. One of the studies reported that topical application of the chamomile solution during the phase of migraine considerably reduced pain scores [106]. Phytoconstituents of chamomile, such as chamazulene and apigenin,may help alleviate migraine headaches by inhibiting the release of nitric oxide [107]. According to recent data, some subjects were sensitive to chamomile suggesting the possibility of allergic reactions.

9.2.5. Lavender (Lavandula angustifolia)

Lavender oil is extracted from the blooming flowers of *Lavandula angustifolia* and consists of primary compounds like linalyl acetate, linalool, lavandulol, 1,8-cineole, lavandulyl acetate, and camphor [108]. The oil is majorly used in aromatherapy and massage. It is applied to the skin undiluted, which is rather rare for essential oils. Reports stated that, lavender has been utilized as a natural remedy and is said to exhibit anticonvulsant, antidepressant, anxiolytic, sedative, and relaxing activities [109]. It has been observed in a study that inhaling lavender oil effectively reduced the intensity of a migraine headache as compared to a placebo [110]. Preclinical studies further showed that lavender reduces inflammation and pain through a number of mechanisms. Generally, lavender is well-tolerated for topical application, but special precaution is advised for those allergic to lavender or in patients with hormone related concerns [111]. More exhaustive research is required to confirm effectiveness of lavender oil in management migraines.

9.2.6. Ginger (Zingiber officinale)

Ginger is a flowering plant known by its rhizome, which is generally called ginger root. It belongs to the Zingiberaceae family and is native to southern and southeastern Asia. Traditional uses of ginger are known, but has been recently confirmed in clinical trials for rheumatic pain, headaches, indigestion and motion sickness [112]. It is effective against migraines and has a history of pain relief and indigestion. Recent evidence indicated that ginger powder may be as efficient as Sumatriptan in the treatment of migraine headache with least side effects [113]. One of the ginger phytoconstituents, Zerumbone acts on cannabinoid receptor CB_1 in the brain to provide relief for migraine sufferers [114]. Considering the role of ginger in migraines, it exhibited antioxidant and anti-inflammatory activities which potentially served as a safe and effective remedy, relieving such symptoms as nausea and vomiting [115].

9.2.7. Brahmi (Bacopa monnieri)

For the last 2000 years, Brahmi is regarded as one of the prominent herbs used in Ayurveda. It is also believed to be a rejuvenating herb. Charak and Sushruta Samhitasdivulged beneficial effects of Bramhi. This herb is known for its soothing and calming effects that reduces stress and allows the body to relax and sleep. It also showed antispasmodic, anticonvulsant, anti-inflammatory, and analgesic properties [116]. These qualities make it beneficial in treating migraines and it is commonly used in Ayurvedic medications. Brahmi is known for its nootropic and

neuropharmacological benefits, which can help in treating memory issues. Other than in medications, Brahmi oil and pastes are used naturally to alleviate migraine pain by massaging onto the scalp or applying into the nostrils [117]. The versatility of Brahmi in tackling the different dimensions of migraine symptoms makes it a potentially useful ingredient in migraine management in Ayurveda.

9.2.8. Ashwagandha (Withaniasomnifera)

Ashwagandha is labelled one of the most respected herbs in Ayurveda for its rejuvenating properties; it can therefore be said to fit into the category of adaptogen, meaning that it helps the body deal with stress. This herb is traditionally used to enhance vigour and may be of interesttherefore, for improving overall physical strength [118]. In addition to its physical advantages, Ashwagandha is also thought to enhance the functioning of the brain and neurological system and this herb may be employed in conditions such as migraine. Its anti-inflammatory properties can aid in the management of migraine conditions by reducing inflammation, which is connected to headache pain in many cases [119]. Research has proved that Ashwagandha helps reduce the level of stress, which is vital since stress is one of the common provoking factors for migraine and can exacerbate its severity.

9.2.9. Feverfew (Tanacetum parthenium L.)

This plant has been traditionally used as an established medicine for some trivial situations namely fever, migraines, and menstrual disorders. Parthenolide, which is majorly present in the leaf, is believed to explain the effect on migraines through inhibiting the production of prostaglandins and exerting an effect on the blood vessels and alterations in serotonin levels [120]. In the end, clinical study evidence regarding Feverfew for migraines showed mixed results, in regard to different dosages and extracts used [121]. Other active ingredients in Feverfew, like chrysanthenyl acetate and melatonin, may aid improve its antimigraine efficacy [122]. This herb is generally safe but can cause mild side effects like oral inflammation and dermatitis. Feverfew affects liver metabolism and has blood-thinning properties, so it must be administered with caution along with other medications.

9.2.10. Butterbur (Petasites hybridus)

Butterbur, a plant from Europe is used in traditional medicine for various conditions like asthma and cancer. Extracts of Butterbur contains compounds like petasitine and tannins. Studies exhibited positive effects of Petadolex® (butterbur extract) on migraine by reducing its frequency of occurrence [123]. Petadolex® is associated with fewer side effects compared to raw butterbur due to the removal of toxic pyrrolizidine alkaloids. The anti-migraine effects of butterbur may involve anti-inflammatory properties and effects on calcium channels [124]. Further research is needed to ensure the safety and efficacy of Petadolex® for migraine treatment.

Fig 8: Herbal Treatments for Migraine

9.3. Preventive Treatment Options

Prophylactic medications decrease the frequency, severity or duration of attacks when acute medications do not suffice. Guidelines from EAN and AAN recommend certain medications, including β blockers, antidepressants, and anticonvulsants. Dose recommendations vary by region and should be guided by local guidelines. Medications are selected based on their effectiveness, capacity to be tolerated by the patient, cost and the patient's personal preference [125]. Regular follow-up is essential to assess the response to treatment and side effects; the dose can be increased or decreased as required. Topiramate, Onabotulinumtoxin A, and monoclonal antibodies have demonstrated efficacy in treating persistent migraines. Monitoring headache episodes associated with pain intensity and its medication leads to an effective evaluation [126]. Following are some classes of drugs employed as preventive therapy for migraine:

9.3.1. Antidepressants

Two antidepressants, Amitriptyline and Venlafaxine, are used in clinical practice. Amitriptyline appears to be efficacious for the prevention of migraines and is comparable to topiramate. There is an inadequate data to support the usefulness of venlafaxine for this purpose. Post-amitriptyline ingestion, individuals frequently experienced weight gain, vertigo and bowel irregularity [127]. Overall, amitriptyline remains extensively utilized in numerous countries worldwide and may be recommended for people with migraines who also have concurrent depression or sleep difficulties [128].

9.3.2. Antihypertensives

These agents are used to treat hypertension along with migraine prophylaxis. β blockers, such as propranolol, metoprololand atenololare extensively recommended all over the globe as the primary drugs for preventing migraines. Various studies indicated that, β blockers, such as propranolol, have proved worthwhile in the prophylaxis of migraine. A study demonstrated that Candesartan, an alternative antihypertensive showed comparable efficacy to propranolol. However, fewer trials have been conducted for Lisinopril in migraine prevention [129]. Antihypertensive agents like Losartan and Amlodipine have a reduced quantum of research contribution towards management of migraine [130]. The choice of antihypertensives to be used for migraine prevention should therefore be based on individual factors and therapeutic response.

9.3.3. Anticonvulsants

Two anticonvulsants, Topiramate and Valproate have equal efficacy in migraine prophylaxis, but their safety profiles differ. Valproate should not be used in pregnant women since it can cause birth defects. Based on a meta-analysis of nine randomized controlled studies, Topiramate was found to be considerably more effective than placebo in reducing the average number of headache days per month [131]. It adversely caused weight loss, asthenia (weakness), nausea, depression, cognitive disturbances (problems with thinking), and paraesthesia (abnormal sensations). Topiramate has also shown an additional benefit in prophylaxis for chronic migraine [132].

9.3.4. Flunarizine

It belongs to the category of drugs known as calcium channel blockers which primarily indicated for use in preventing migraine headaches in some countries. Notably, Flunarizine is not approved for use in the US which may preclude people who require treatment for migraine

prophylaxis [133]. In comparative analysis, RCTs have proved Flunarizine to be effective in providing clinical benefit for the prevention of episodic migraine.Use of Flunarizine is commonly associated with adverse effects such as weight gain, exhaustion, nausea and constipation. It is important to notethat Flunarizine can also cause drug-induced parkinsonism, a severe adverse reaction in some patients [134].

9.3.5. Onabotulinumtoxin A

is effective in preventing chronic migraine but did not demonstrate any significant difference compared to placebo for episodic migraine. It was found to have a higher level of tolerability compared to Topiramate in a single trial withfewer dropouts due to lack of effectiveness or side effects. No systemic adverse events have been reported using Onabotulinumtoxin A [135].

9.3.6. Anti-CGRP monoclonal antibodies

The function of calcitonin gene-related peptide in migraine pathophysiology has led to the development of four monoclonal antibodies that target CGRP (Fremanezumab, Galcanezumab and Eptinezumab) or its receptor Erenumab with similar efficacy and safety and tolerability for episodic and chronic migraines. Erenumab is administered at a dose of 70 or 140 mg once monthly subcutaneously, Fremanezumab is given at a dose of 225 mg once 30 days subcutaneously [136], Galcanezumab 120 mg once 4 weeks subcutaneously with a 240 mg loading dose [137], and Eptinezumab 100 or 300 mg once quarterly intravenously [138]. Of note, Fremanezumab may also be given quarterly in higher doses. These antibodies are active, even in individualswith failure of two or more preventive medications because of efficacy or tolerability issues [139]. The most frequently occurring adverse events are reactions at the injection site—pain and erythema—mainly in Erenumab, which can cause constipation. However, possible immunogenicity and theoretical concerns about cardiovascular safety have to be taken into consideration. Data for follow-up at six months are currently limited in patients treated with CGRP monoclonal antibodies [140]. Presently, there is limited clinical use of these therapies due to their high costs and regulatory requirements mandating documented failure with at least two other preventive medications.

9.4. Non-pharmacological Treatment Options:

Non-pharmacological interventions provide advantages for those suffering from migraines and can be utilized either independently or in conjunction with pharmacological treatments. Such treatments add a multidisciplinary approach to clinical management with rationale use of drugs [141]. The most compelling data supports the effectiveness of cognitive-behavioral therapy (CBT), biofeedback, and relaxation training as the most effective neuromodulation and biobehavioral therapies. Nonetheless, weak supporting evidencesare available for physical therapy, sleep management, acupuncture, and dietary modifications [142].

9.4.1. Neuromodulatory devices

Neuromodulation for migraine includes implantable and non-invasive devices. Implantable devices are highly controversial with modest benefit. Nevertheless, non-invasive neuromodulatory techniques proved advantageous and were well-tolerated by those suffering from migraines. Indeed, the FDA has approved several non-invasive treatments for both acute and preventive

treatment, including single-pulse transcranial magnetic stimulation (sTNS) [143] and external trigeminal nerve stimulation (eTNS) [144]. In addition, neuromodulators, such as noninvasive vagus nerve stimulation and remote electrical neuromodulation, have been approved for treating acute migraine. However, evidence remains to be provided regarding the long-term effects of neuromodulation. With the advancement of research in neuromodulatory devices, encouraging treatment alternatives are available adjunct to pharmacological therapy.

9.4.2. Bio-behavioural therapies

These therapies, such as CBT, relaxation training and biofeedback, play an essential role in migraine management. The American Headache Society (AHS) recommends these therapies for preventive migraine treatment, backed by Grade A evidence. In comparison to 24% of controls, 54% of migraine patients who received psychological therapy reported at least a 50% reduction in migraine frequency, according to a meta-analysis by The Cochrane Collaboration [145]. Interestingly, this Cochrane review differs from conclusions drawn in another systematic review and partly aligned with the guidelines for clinical trials. To enhance study designs and ensure consistent reporting of outcomes, pragmatic solutions should be implemented [146]. Nevertheless, biobehavioral therapies remain an important treatment option for patients, including those with psychological symptoms or specific considerations like pregnancy or a preference for non-pharmacological approaches [147].

9.4.3. Dietary approaches

The focus on dietary management for migraines is popular among some individuals and media outlets. Common dietary approaches include elimination diets and avoiding specific triggers. However, there are limited evidences supporting the impact of dietary interventions on migraines. Considering avoidance of dietary triggers, clinicians should be cautious about attributing causality to specific foods in migraine development [148]. Similarly, ascribing beneficial effects to specific diets prematurely is unjust, as studies have shown benefits from both intervention diets and control diets. Current studies with limited evidence stated that weight loss is related to a decrease in headache frequency in those with migraine [149]. Good quality evidences are required to establish the role of dietary interventions in the clinical management of migraines.

9.4.4. Physical Therapy

Although many people with migraines also have widespread musculoskeletal pain, the extent to which physical therapies have to offer is under investigation. Some studies have shown that such therapies could improve clinical outcomes, but a randomized controlled trial showed no additional benefits of physical therapy as an adjunct to migraine medications [150]. Another meta-analysis of controlled trials found out that physical therapy techniques decreased the duration of the migraine attack, while the calculated effects on pain intensity and attack frequency were insignificant [151]. The conclusions regarding the effectiveness of physical therapy in patients with migraine are thus evident.

9.4.5. Quality of sleep

Poor sleep quality is a common complaint among patients with migraines. 46% of the patients with migraines reported experiencing insufficient sleep, while only

20% of the control group without headache disorders claimed the same [152]. In contrast to its incidence, sleep management for migraines is understudied. A limited number of randomized controlled trials (RCTs) have been carried out, demonstrating the effectiveness of CBT for improving sleep in individuals with chronic migraine and associated insomnia [153]. Future studies should involve comparative analysis of effectiveness linked with various sleep therapies.

9.4.6. Acupuncture

The use of acupuncture for migraine has been a topic of debate for two decades, with no clear consensus. Whereas three huge RCTs established minimal benefit of acupuncture against sham acupuncture. In 2016, a Cochrane review indicated that acupuncture might decrease the frequency of headaches in people who have episodic migraines when used in conjunction with acute medications [154]. However, evaluating acupuncture is challenging due to limitations related to sham acupuncture procedures (which avoid acupuncture points and often use fewer penetrative needles). Most available data is inherently biased, potentially attributing benefits to a placebo effect. Nevertheless, acupuncture has some side effects and can be used as an alternative, if the patient does not respond to preventive medications or has some contraindications for the same [155].

Conclusion

Exploring about migraines and their multifaceted nature, a neurological disorder most likely with recurrent, moderate to severe headaches and in the majority of cases certain accompanying symptoms, has been defined. The significance of migraine in both individuals and society as a whole has been emphasized by examining its prevalence, forms, causes, symptoms, and current treatment options. Migraine is well understood in its different manifestations, considering it the very cornerstone for the realization of effective management and treatment. One of the most significant findings were observed that the treatment has to be personalized, focusing on the uniqueness of every patient suffering from migraines. From the pharmacological acute to preventive interventions, the treatment modalities shift towards non-pharmacological interventions, including alternative treatments, of which diversity is most likely based on the complexity of the disorder itself. Furthermore, still under investigation, the pathophysiology of migraines revealed complex mechanisms responsible for triggering a severe headache attack, due to genetic and neurochemical imbalances, as well as environmental factors. Adhering to the explored facts manifesting migraine advances in its management and prevention remains predominant. Therefore, a strong forward driver for detailed research associated with complexities in the pathogenesis of migraine should be undertaken to craft specific and efficacious treatment regimens. Developments in the treatment of migraine are crucial for both symptomatic relief and minimizing the long-term effects on the quality of life for those who suffer from the condition. In addition to scientific research, awareness in the general population must be spread regarding migraine as a serious neurological disorder. Elevation in awareness by the general populace and healthcare providers would enable earlier diagnosis, proper treatment, and hence improved outcomes for those affected individuals. In addition, it creates a more empathetic and supportive enclosure for people with migraines, rather than

stigmatizing them. This review thus highlights migraine and its molecular mechanisms with a wide variety of treatment alternatives aiding health care professionals to design a unique personalized treatment regime.

Declaration

Conflict of Interest

The authors did not declare any potential conflict of interests

Acknowledgement

Dhanashree Wasu and Dr. Shilpa Chaudhari extend gratitude to the Principal, Dr. D Y Patil College of Pharmacy, Akurdi, Pune for the constant encouragement.

Dhanashree Wasu extends gratitude to the Principal, Nagpur College of Pharmacy, Higna, Nagpur for the guidance and support.

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