

A Review Article on Migrane

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ABSTRACT:

Migrane are a neurological disorder characterized by recurrent, moderate to severe headache. They are often accompanied by symptoms such as nausea, vomiting, sensitivity to light and sound and in some cases, visual disturbances migraines can significantly impact a person's quality of life and may require a combination of lifestyles changes, medication and other therapies for effective management. Migraine is the sixth most prevalent disease globally, a major cause of disability, and it imposes an enormous personal and socio-economic burden. Migraine treatment is often limited by insufficient therapy response, leading to the need for individually adjusted treatment. In this review, we analyse historical and current pharmaceutical development approaches in acute and chronic migraine based on comprehensive and systematic analysis of Food and Drug Administration (FDA)-approved drugs and those under investigation. The development of migraine therapeutics has significantly intensified during the last 3 years, as shown by our analysis of the trends of drug development between 1970 and 2020. The spectrum of drug targets has expanded considerably, which has been accompanied by an increase in the number of specialised clinical trials. This review highlights the mechanistic implications of FDA approved and currently investigated drugs and discusses current and future therapeutic options based on identified drug classes of interest

KEYWORD: Migraine, Types Of Migraine, Pathophysiology, Diagnosis, Classification, Treatment.

Introduction:

Migraine is the most frequent neurological problem in Primary Care. According to the findings of the last Global Burden Disease study, migraine continues second among the world's causes of disability, and first among young women [1]. Migraine is a frequent disorder as it affects 18% of women and 6% of men, while chronic migraine affects 2% of the global population, and it is extremely burdening condition for the patients, their families and the society [2]. Migraine is a common chronic headache disorder characterized by recurrent 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 [3]. The study of migraine in the pediatric population is critical because of its burden on children and their families and the diagnostic and therapeutic difficulties determined by varying phenotype and possible differential diagnosis [4].

Types of Migraine:

Migraine, a complex neurological disorder, manifests in various forms, each presenting distinct clinical characteristics.

1. **Migraine with Aura:** Migraine with aura involves transient neurological symptoms preceding the headache, often visual disturbances. In contrast, migraine without aura is marked by pulsating headaches accompanied by symptoms like nausea and sensitivity to light and sound.
2. **Chronic migraine:** Chronic migraine poses a significant health burden, defined by headaches occurring on 15 or more days per month.
3. **Menstrual migraines:** Menstrual migraines are closely linked to the menstrual cycle, presenting challenges in management.
4. **Vestibular migraines:** Vestibular migraines contribute to the diversity, incorporating symptoms of dizziness and balance disturbances.
5. **Hemiplegic migraines:** Hemiplegic migraines, though rare, are characterized by temporary paralysis.
6. **Retinal migraines:** retinal migraines involve transient vision loss in one eye[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 [7].

Pathophysiology:

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	<ol style="list-style-type: none"> 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].

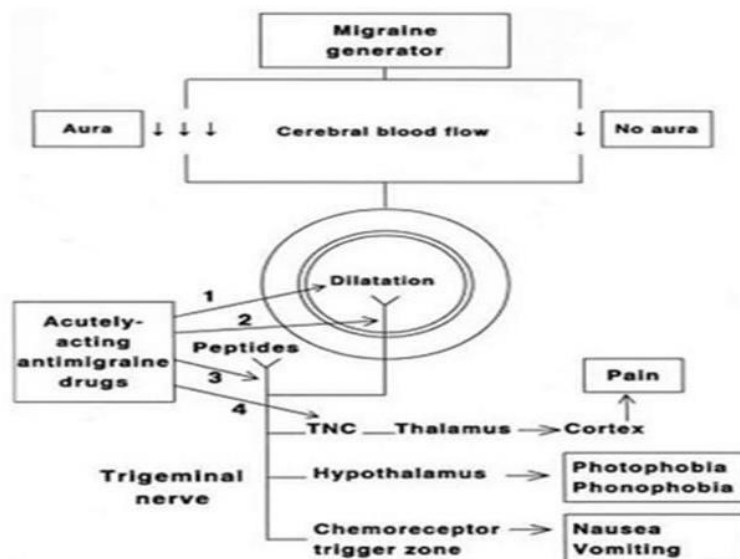
Table 1

1. Vascular and Neurogenic theories

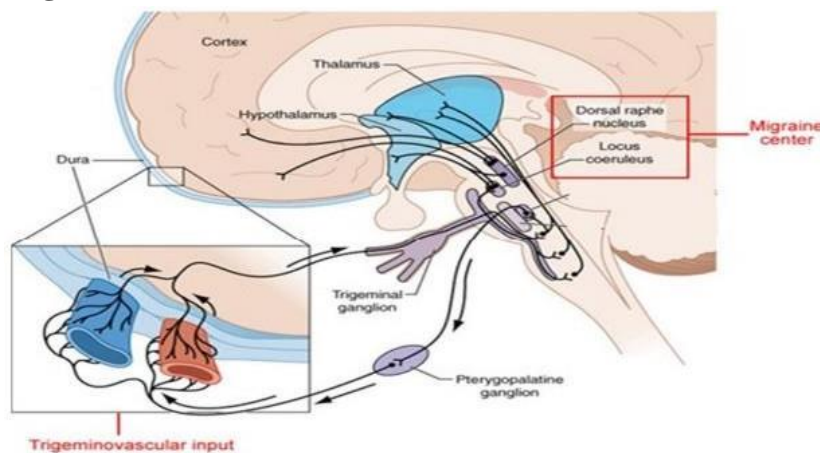
The cause of migraine headache is still not completely understood. Historically, two independent theories, the vascular theory and the neuronal theory, explaining the etiology of migraine headache were proposed. The vascular theory was introduced by Thomas Willis where he recognized that “all pain is an action violated” and argued the pain from headache is caused by vasodilatation of the cerebral and meningeal arteries. The alternative neurogenic theory focuses on the cause of migraine pain and is currently linked to activation of the trigeminovascular system. [8]

2. Cortical Spreading Depression

The alternative and widely accepted theory suggests that cortical spreading depression (CSD), a wave of neuronal hyperactivity followed by an area of cortical depression, accounts for the aura and that the headache depends on activation of the trigeminovascular pain pathway. In Chronic Migraine (CM), atypical pain processing, central and peripheral sensitization, cortical hyper excitability, and neurogenic inflammation all have a role to play. Cortical hyperexcitability is thought to be another major factor participating in transformation of EM to CM[9].



Pathophysiology of migraine



Perivascular trigeminal C-fibre endings are stimulated to release vasoactive neuropeptides like substrate P, neurokinin A and calcitonin gene-regulated polypeptide (CGRP) leading to a sterile inflammation.

Lifestyle modifications for migraine:

When seeing a child with migraine it is essential to discuss and address potential lifestyle changes that may be contributing to headache frequency and how these can be managed and modified in order to prevent further progression of migraine.

- **Sleep**

Although it can be very difficult to establish and maintain regularity and homeostasis of a daily routine in childhood and adolescence, unpredictability and changes in daily schedules can be related to an increase in migraine frequency [10]. Therefore, the first step in migraine prevention is always counseling children and their families on proper lifestyle management. It is important to encourage adequate amounts of sleep for age as well as a consistent sleep schedule that does not vary weekday to weekend. Adolescents have a physiologic sleep phase delay that causes them to stay up later and sleep in later as well [11]. New recommendations from the American Academy of Pediatrics state that high school should begin no earlier than 8:30 am; [12] however, only 17.7% of schools in the USA actually abide by this time frame.

- **Hydration**

The second aspect of lifestyle that children and adolescents are encouraged to focus on is hydration. In a random sample of children and adolescents aged 6–19 years, 55% of them were found to be mildly dehydrated based on their urine concentrations [13]. Increasing water intake has been shown to be associated with improved headache severity in adults with headache [14]. It is important to advise to have a water bottle at school with them at all times. Similarly, fasting can provoke migraine [15]. and so, it is important to encourage children and adolescents with migraine to have portable snacks with protein on hand.

- **Physical activity**

The incorporation of regular physical activity is essential when discussing lifestyle as well. In an adult study, aerobic exercise for 40 minutes three times a week was shown to improve the frequency and severity of migraine attacks equally as effective as some preventive medications [16].

Early life predictors of migraine:

A number of predictive childhood factors have a strong correlation with migraine later in life. Many of these are thought to potentially represent early life manifestations of migraine, others are unique or rare subtypes of pediatric migraine [17]

- **colic**

Infantile colic typically presents from birth to 4 months of age, characterized with recurrent episodes of irritability, fussiness, or crying that can last at least 3 hours a day, occur on 3 days a week for at least 3 weeks. Children with migraine are more likely to have experienced infantile colic, and women with migraine are more likely to have a baby with colic. In addition, babies with colic are at a higher risk to develop migraine without aura as adolescents [17].

- **other episodic conditions**

There are three episodic conditions that are very closely related to migraine. Benign paroxysmal torticollis affects older infants; it presents with periodic attacks of head tilt, nausea, vomiting, fussiness and at times ataxia in older toddlers. It has been shown to be associated with the CACNA1A gene, associated with one subtype of hemiplegic migraine [18]. Benign paroxysmal vertigo affects children in their pre-school age; it presents with periodic attacks of vertigo that typically last for several minutes. Cyclic vomiting syndrome is a diagnosis most commonly seen in elementary school age children; it presents

with periodic attacks of frequent vomiting that are occasionally accompanied by abdominal pain and anorexia. Also of note is the fact that the presence of nausea accompanied by headache in children is the strongest predictor of missing school [19].

Diagnosis:

Diagnosis of Migraine can be made through history taking alternatives are rule out with help of orthopedic tests, Cranial nerve examination, Complete blood count, urinalysis and Cranial magnetic resonance imaging was performed if required. [20] The International Classification of Headache Disorders defines the migraine by following criteria. [21]

A. At least five attacks 1 fulfilling criteria B–D

B. Headache attacks lasting 4-72 hours (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 physical activity., walking.

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.

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[22].

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 worsen by some routine physical activities and is associated with nausea photophobia and/or phonophobia [23].

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 [23]

Migraine with typical aura:

Migraine with aura, in which aura consists of any of the following 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. Typical aura with headache: Migraine with typical aura in which aura accompanied by with or without migraine characteristics and followed within 60 minutes by headache.[23]

Quality of life:

UK research

In addition to impacts of physical and mental health, migraine may also affect people's quality of life. There is limited published research about the quality of life of people living with migraine in the UK. A small number of comparative studies have suggested that people living with migraine have lower general and health related quality of life than others.[24] A study comparing people from the UK and the USA found that people living with migraine in both countries had lower health related quality of life than people without migraine [25] In another UK study, 106 people living with migraine were surveyed about the level of pain they experienced during an attack and their health status. The researchers found that mild, moderate and severe migraine pain were all associated with reduced health related quality of life. The more severe the pain, the worse people reported their quality of life was.[26]

Home life:

UK research

Research has also been conducted into the impact of migraine on the family members of those living with migraine. One study, interviewed people living with migraine and their partners. More than 1000 people from England and the USA took part. People with migraine and their partners said that migraine impacted on family life and relationships. Those living with migraine said they:

- were less able to do housework and chores than people without migraine (85%)
- missed family social and leisure activities (45%)
- avoided making plans in case they needed to cancel them due to migraine (32%)
- were more likely to argue with their partners (50%) and children (52%) Up to 60% of partners reported that migraine had negative effects on their relationships and also meant that they were required to do more work around the home. There was no difference in the findings between countries [27].

Emerging Acute Therapies:

• 5-HT_{1F} Receptor Agonists:

Triptans are serotonin 5-HT_{1B/1D} receptor agonists and have remained the mainstay of acute migraine treatment since their introduction.[28] Despite evidence to the contrary,[29] the potential for vasoconstriction associated with their use has curbed their widespread usage over concerns of cardiovascular and cerebrovascular risks. Ditans are a new class of serotonin 5-HT_{1F} receptor agonists that were developed to treat acute migraine. Lasmiditan was the first medicine to be introduced and approved by the FDA for the acute treatment of migraine with or without aura.[30]

• CGRP Receptor Antagonists and Gepants:

In the 1990s, a class of serotonin 5-HT_{1B/1D} receptor agonists, the triptans, were introduced as acute therapy in migraine management.[31] However, the potential vasoconstrictor effects associated with their use in patients with cardiovascular and cerebrovascular diseases had prevented their widespread use.

[32,33] Studies had shown that CGRP levels were elevated in the jugular vein during spontaneous and provoked migraine attacks. Provocation studies that used CGRP had shown that it could induce migraine-like attacks in migraineurs that subsided after they were given triptans.[34,35] Against this background, interest turned to the development of gepants.

- **Ubrogepant**

Ubrogepant has completed 2 positive phase 3 studies (ACHIEVE I and II). In Achieve I, 1327 patients were randomised to placebo, ubrogepant 50 mg and 100 mg. [36] The study met the primary endpoints of relief from pain for 2 hours and absence of most bothersome symptoms for both doses compared to placebo. Achieve II randomised 1355 patients to a lower dose of 25 mg and 50 mg [37]. Both doses showed statistically significant results in providing relief from pain for 2 hours compared to placebo, while the 50 mg dose provided absence of most bothersome symptoms for 2 hours.

- **Rimegepant**

The findings of the latest phase 3 trial that assessed the efficacy of rimegepant in the treatment of acute migraine against placebo were published in July 2019. The results were positive: 19.6% of patients were pain-free for 2 hours after taking rimegepant compared to 12.0% in placebo. Likewise, for freedom from most bothersome symptoms at 2 hours post-dose, it was 37.6% in rimegepant patients compared to 25.2% in placebo [38].

Treatment:

Variety of drugs has been specifically designed to treat migraines. Medications used to combat migraines fall into broad categories:

- A. Pain-relieving medications** They are also known as acute or abortive treatment; these types of drugs are taken during migraine attacks and are designed to stop symptoms that have already begun.
- B. Preventive medications** These types of drugs are taken regularly, often daily basis to decrease the frequency or severity of attacks.

Pain relieving medication:

For best results, take pain-relieving drugs as soon as you experience signs or symptoms of a migraine. It may help if you sleep or rest in a dark room after taking them.

- **Pain-relievers**

Medications like ibuprofen; acetaminophen may help relieve mild migraines. Drugs marketed specifically for migraines like combination of acetaminophen, aspirin and caffeine may ease moderate pain but are not effective for severe migraines. If taken for long periods, these can lead to ulcers, gastro intestinal bleeding and rebound headaches.[39]

- **Triptans**

Triptans are the drug of choice with people of migraine attacks. They are effective in relieving the pain, nausea, sensitivity to light and sound associated with migraines. Medication includes drugs like sumatriptan, rizatriptan, almotriptan, zolmitriptan, frovatriptan and eletriptan. Side effects are nausea, dizziness and muscle weakness. They are not suitable for people at risk for strokes and heart attacks. Combination of sumatriptan and naproxen sodium (treximet) has proved effective in relieving migraine symptoms than individual medications.[40]

- **Ergot**

Combination of ergotamine and caffeine (migrergot, cafergot) are less expensive and also less effective

than Triptans. They are most effective where pain lasts for more than 48hrs. Dihydroergotamine is more effective and has fewer side effects than ergotamine. It is also available as nasal spray and in injection form.[41]

Preventive medications:

Nearly half of those who get the migraines could benefit from preventive medication. Only one in ten people take it. The patient can approach this therapy if he has two or more deliberate attacks a month. This therapy can reduce the frequency, severity and length of migraines. Doctor may recommend taking the preventive medications daily or only during a predictable trigger such as when menstruation is approaching. Some of the drugs used in preventive treatment are:

- **Cardiovascular drugs**

Beta-blockers commonly used to treat high blood pressure and coronary artery disease can decrease the frequency and severity of migraines. These are considered as the first line treatment drugs. Calcium channel blockers like verapamil are also helpful in preventing migraines and relieves from aura. Anti-hypertensive medications like lisinopril, candesartan are useful in decreasing the frequency and severity of migraines. The side effects include dizziness, drowsiness or lightheadedness [42]

- **Anti-depressants**

Tricyclic antidepressants like amitriptyline, nortriptyline and protriptyline are most effective in preventing certain headaches including migraines. They act by affecting the level of serotonin and other brain chemicals.

- **Anti-seizure drugs**

Some anti-seizure drugs such as divalproex and topiramate and gabapentin reduce the frequency of migraines. These drugs may cause side effects like nausea, vomiting, diarrhea, cramps, hair loss and dizziness at high doses.[43]

- **Cyproheptadine**

These anti-histamines specifically affect the serotonin activity. Physicians sometimes give it to children as a preventive measure.

- **Botulinum (toxin type A)-Botox**

Sometimes it is used as treatment for chronic migraines. Injections are made in the muscles of forehead and the neck. When this is shown to be effective, the treatment typically needs to be repeated every 3 months [44,45].

Ayurvedic treatment:

Besides the availability of a wide variety of painkillers off-the-shelf for migraine, they may not always work because the remedy lies in the cause of migraine. Pain relievers help only to suppress the pain but the problem still persists in the body. Side effects like depression, anorexia, high blood pressure, giddiness and ulcer may be seen. [46,47]

Home remedies for migraine:

Caffeine: Caffeine hinders headache as it is a double-edged sword. Caffeine restricts blood vessels, reduces pain. It is a constituent of pain over-the-counter pair medicines but has to be taken limitedly, because if taken excessively, it leads to rebound headache, thus making existing headaches worse.

Water: Dehydration is a big cause for headaches. Hence drink water as much as possible.

Tie A Head Band Around Head: It is a practice that has been done since ancient times.

Peppermint Oil: Take some peppermint oil and rub it on the part of head that hurts.

Fish Oil: Fish oil works by restricting the blood vessels in brain and reduce inflammation.

Ginger: Eating ginger or ginger capsules may help sometimes. It also reduces nausea clearly.

Magnesium: Menstrual associated migraines and migraines associated with auras can be markedly reduced by the intake of Magnesium in dose of 400- 600mg/day. Caution: when taken excess it results in diarrhea.

Riboflavin: Vitamin B2 can also prevent migraine in dose of 400mg/day. Dose has to be adjusted because it causes frequent urination or might cause darker urine.

Coenzyme Q10: It is effective in reducing headache when taken 300mg/day [48].

Conclusion:

Despite being one of the most disabling headaches, migraine is still underdiagnosed and undertreated. It is unequally distributed among people of mental and physical work, different socioeconomic levels, and residents of the city and the urban regions. Earlier, it was believed that more educated people and urban dwellers were more likely to suffer from migraine. However, contemporary studies have shown that this pattern can be traced only in the population of patients seeking treatment. It turns out that more educated patients are more worried about their headaches and are more likely to consult a doctor. In the general population of patients, these differences are not preserved. Migraine was found to be more widespread in women than men as well as more predominant in the urban population. Furthermore, it potentially influences the daily life activities of the patients, including social occasions, employment, and schooling. (is forms a challenge not only for the patients but also for physicians with respect to appropriate recognition, prevention, and timely treatment) therefore, longitudinal studies are needed in the future in investigating the prognosis and predictors of chronicity in the Arab countries to retrieve more accurate results.

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