Review Article

Migraine with Different Phases and Various Therapies Used to Treat Migraine

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ABSTRACT

Migraine is a complex neurovascular headache disorder characterized by moderate to severe headache episodes, often accompanied by symptoms like phonophobia, nausea, and vomiting. The biology of migraine involves genetic predisposition, environmental factors, and sensory brain processing. Episodic migraine (EM) occurs fewer than 15 headache days per month, while chronic migraine (CM) occurs 15 or more days per month. CM usually develops from EM with a yearly advancement rate of 3%, and risk factors include high baseline frequency of EM attacks, acute drug overuse, and comorbid mental illnesses. Migraines affect relationships, work, financial well-being, and physical and mental health. Pathophysiology involves activation of the trigemino-vascular system and hypothalamic involvement. Treatment aims to improve patient function, with options like triptans, ditans, gepants, ergot alkaloids, NSAIDs, and analgesics. Triptans, developed in the 1990s, work by activating serotonin receptors, while ditans like lasmiditan target 5-HT1F receptors. Gepants, such as ubrogepant, are CGRP receptor antagonists. Ergot alkaloids, like dihydroergotamine, have been used since the 1920s and work as non-specific 5-HT1 receptor agonists. Understanding these mechanisms can help develop targeted therapies for migraine treatment.

Keywords: Migraine treatment, triptans, ditans, gepants, ergot alkaloids, CGRP-related mechanisms.

1. INTRODUCTION

A chronic neurovascular headache condition, migraine is usually characterised by moderate to severe headache episodes that are accompanied by phonophobia, nausea, and vomiting [1]. About three fourth of migraineurs have a premonitory period before the headache starts, and about one third suffer migraine with aura [2]. The biology of migraine is complex, diverse, and in some cases, yet unclear. The underlying characteristic appears to be a complicated genetic predisposition coupled with environmental and behavioural factors that modify sensory brain processing and increase sensory receptivity. Consequently, migraineurs perceive apparently normal sensory stimuli as uncomfortable [3]. Episodic migraine (EM) is the term used to describe migraineurs who have fewer than 15 headache days per month. A headache that occurs 15 or more days a month for more than three months and exhibits migraine symptoms at least eight days a month is referred to as chronic migraine [4]. With an approximate yearly advancement rate of 3%, chronic migraine usually develops from episodic migraine [5]. Risk factors for advancement include a high baseline frequency of episodic migraine attacks, acute drug overuse, obesity, stressful life events, female gender, and poorer socioeconomic position. The mechanisms behind the transition from episodic to chronic migraine seem to be complex. Furthermore, comorbid mental illnesses including anxiety and depression are more common in people who suffer from chronic migraines. These disorders demonstrate the complex nature of the chronic migraine disease by maintaining and increasing migraine frequency and intensity in the opposite direction [5]. All facets of life, including relationships, work, financial well-being, and physical and mental health, are negatively impacted by migraine, which can be fatal [4].

2. HISTORY OF MIGRAINE

About 15% of people in the US suffer from migraines, a chronic neurological condition that has significant negative effects on both personal and financial lives. According to the World Health Organisation, migraine is the primary cause of disability among women aged 15 to 49 and the second most common cause of years lived with a disability. One way to evaluate the standard of continuing medical care and spot obstacles to improved results is to track patterns of consultation, diagnosis, and treatment [6]. Migraines are more common in women than in males, and their prevalence rises as household income, a measure of socioeconomic position, falls. After controlling for socioeconomic position and other factors, the prevalence of migraine is higher among White people than among Black and African American people. The age-adjusted frequency is lowest among Asians, comparable among Whites, Blacks and African Americans, and Latinx people, and highest among Native Americans, according to research that did not take socioeconomic factors into consideration[4]. Migraines are one of the main causes of years lived with disability globally, according to the Global Burden of Disease research. It has not been demonstrated that race or income are independently connected with the degree of migraine-induced impairment. Nonetheless, sociodemographic variations in migraine diagnostic and treatment trends suggest that these variables might affect the probability of obtaining the right migraine therapy [4]. According to literature reviews, 64–77% of persons have had a headache. Between 46% and 53% of adults suffer headaches annually. Although the survey method varies, researchers have shown that lifetime headache prevalence ranges from 8% to 96% [7].

3. FACTORS RESPONSIBLE FOR MIGRANE

Children, adults, and the elderly are all afflicted by the lifelong ailment known as migraine. Age-dependent differences in migraine's clinical presentation include shorter duration, the occurrence of unique paroxysmal symptoms in children, such as nausea, vertigo, or stomach pain, and, in the elderly, a general lack of autonomic symptoms. Migraines in children can range from 2.7% to 10.0%, depending on the study and age group. In children under 7, boys and girls have similar migraine rates. Oestrogen withdrawal can produce menstrual episodes in women, which may explain why migraine is more common in women than males throughout reproductive years. After menopause, women report fewer migraines, suggesting hormonal changes are more important. Migraines affect 3.5% of older persons, and women are twice as likely as men. Many causes can induce migraines, but stress and sleep deprivation are particularly common [8]. About 70% of migraine patients indicate that stress triggers acute episodes, making it a regular occurrence among them. Stress is first among the known triggers of migraine episodes in terms of frequency. A closer look at the association between stress and migraines reveals that these two have more complex dynamics in common. Three different migraine patient clusters, each with a slightly different pattern, are revealed by stress–migraine temporal alignment. Stress levels rise during the migraine pain phase when viewed at the aggregate group level. Another potential contributing component to the aetiology of new-onset migraine is psychological stress. Even though numerous studies show a favourable correlation between stress and migraine, rising stress typically results in an increase in migraine frequency and intensity [9]. Studies on twins and families have shown that a person's vulnerability to migraines is influenced by genetic variables. For those who suffer from monogenic migraine diseases, like FHM, where a pathogenic variation in a single gene can cause the disorder with almost total penetrance, this is evident. According to twin and family studies, the heritability of common migraine is believed to be between 30 and 60% [10].

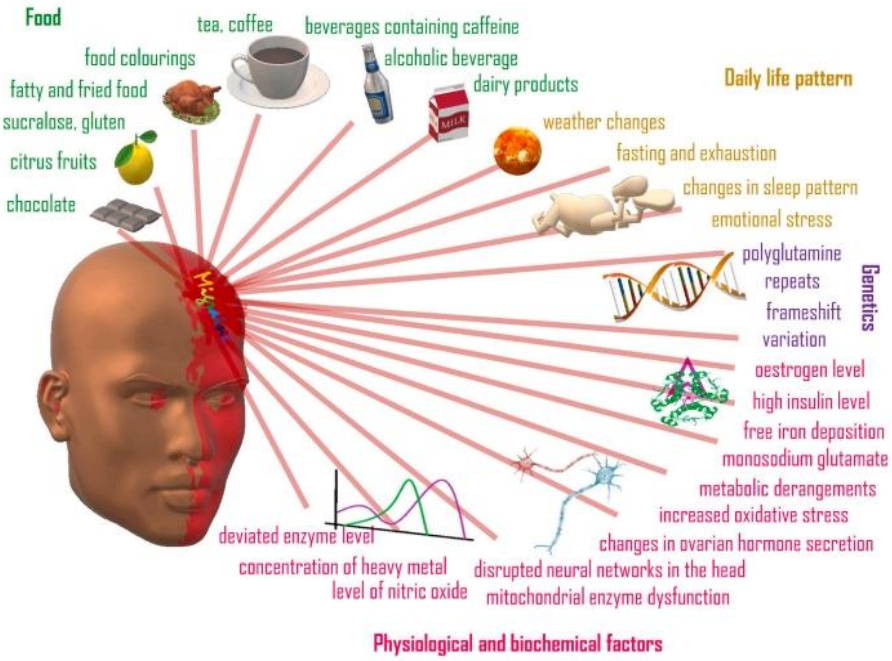

Figure 1: Factors that trigger migraine [11].

4. PATHOPHYSIOLOGY OF MIGRAINE

Migraine is only caused by the vasculature to take into account intricate nociceptive structures and tissue excitability in its pathophysiology [11]. According to the current neurovascular theory of migraine, migraine attacks are initiated and driven by the activation of the trigemino-vascular system (Goadsby and Edvinsson, 1993). In this regard, the hypothalamus may be involved in migraine attacks, according to clinical and neuroimaging findings. Considering May and Burstein have hypothesised that variations in the connectivity between the hypothalamus and other pertinent areas of the brain for migraine (such as the dorsal rostral pons nuclei, spinal trigeminal nuclei, and thalamic neurones projecting to the cortex) over time may explain the preictal (prodromes) and ictal (head pain, accompanying symptoms, and emotional aspects of headache) of migraine, as well as migraine termination. According to May and Burstein (2019), the same authors proposed that "spontaneous oscillations of these complex networks lead to changes in the susceptibility thresholds for migraine attack," which could play a role in the onset, maintenance, and cessation of migraine attacks [12]. Every headache attack has a different set of symptoms, making migraines cyclical disorders. The hallmark of migraine in its episodic form is recurrent episodes that occur in phases:

(a) A premonitory period that precedes the actual headache and is marked by symptoms including increased yawning,

thirst, drowsiness, appetite, mood swings, and cognitive impairments.

(b) Before the headache actually begins, there are brief neurological symptoms called migraine aura, which are usually visual changes.

(c) A severe headache attack that typically affects just one area of the head, is made worse by movement, and is accompanied by nausea and hypersensitivity to light and scents.

(d) The postdrome phase, which is primarily defined by neck stiffness, weariness, and trouble focussing and understanding. Patients may seem normal during the interictal phase, but they are vulnerable to an attack due to a combination of triggers and hereditary predisposition [8]

4.1 Premonitory Phase:

When patients exhibit premonitory symptoms (PS), which are defined by the third edition of the International Classification of Headache Disorders, beta version (ICHD-3 beta) as occurring before the aura in migraine with aura and before the onset of pain in migraine without aura, the premonitory phase of migraine is the one that occurs before pain. One Fatigue, exhilaration, depression, increased hunger, or cravings for a certain cuisine are a few examples of PS. It is not advised to use terminology like "prodrome" or "warning symptoms" because they are unclear and have other uses [13].

4.2 Aura Phase:

A headache attack frequently precedes a migraine with aura, a subtype of migraine that manifests as visual, sensory, or central nervous system symptoms. Cortical spreading depression (CSD) and a reduction in regional blood flow in the cortex are associated with these symptoms [11]. One-third of migraineurs experience this stage. The aura phase, also called cortical spreading depression (CSD), is characterised by two primary pathogenic mechanisms: depolarisation of the brain and the formation of a transitory wave. It has been demonstrated by researchers that this process is the primary cause of the aura phase. The visual cortex's retinotopic propagation suggests that CSD may play a part in migraine. This is the aura phase's primary distinguishing trait [14]. Evidence from family and cohort epidemiology studies shows that the genetic contribution is highest in migraine with aura [15].

4.3 Headache Phase:

The headache phase is characterised by moderate to severe unilateral pulsing pain. The neurovascular theory explains this pain by stating that higher cerebral centres like the thalamus and hypothalamus have an earlier activity that triggers the activation of the trigemino-vascular system [14]. It is commonly acknowledged that the activation of the trigeminovascular pathway is the cause of the throbbing pain that characterises migraine headaches. The distribution of migraine pain is explained by the anatomy and physiology of the well-characterized trigeminovascular circuit [16].

4.4 Postdromal Phase:

It can occasionally be a continuation of the same pathology or a different stage of the illness. Symptoms such as fatigue, weakened muscles, mood swings, difficulties focussing, and decreased appetite may be reported by patients [14]. While some of these symptoms appear during headache treatment, patients frequently incorrectly think they are a side effect of the acute drug while they are a component of the attack [17].

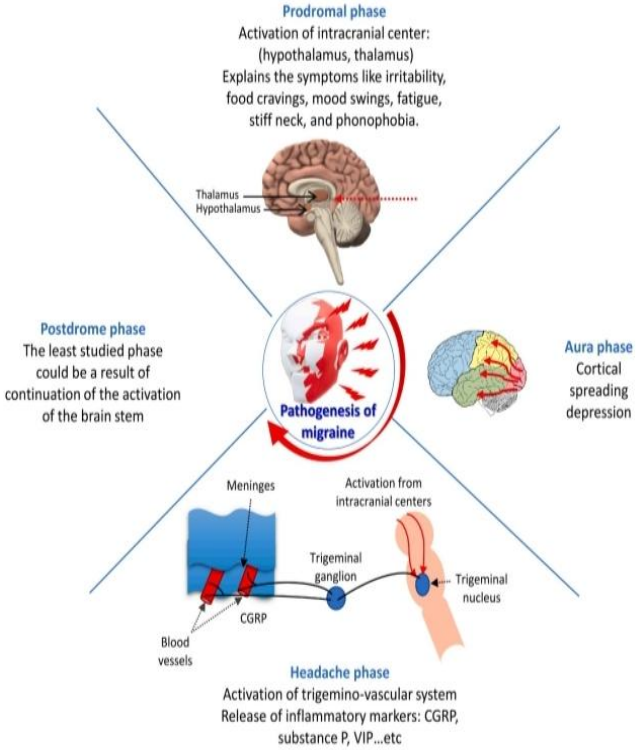

Figure 2: The mechanisms of the different phases of migraine [14].

5. DIGNOSIS OF MIGRAINE

The International Classification of Headache Disorders (ICHD-3) third edition divides migraine into three primary categories: chronic migraine, migraine with aura, and migraine without aura. To guarantee an appropriate diagnosis, each's clinical features must be considered [18]. The foundation for diagnosing migraines is the medical history, with the help of many published tools, a comprehensive medical history should allow for the methodical application of the ICHD-3 criteria. Most of the time, physical examinations are confirmatory, but occasionally, further tests (such as neuroimaging, blood work, or lumbar puncture) are needed to confirm or rule out secondary headache causes [18].

Migraine is Dignosed by some characteristic features like,

- Moderate to severe pain
- Duration of 4 hours to 3 days

- Periodic occurrence; several per month to several per year
- Located on one or both sides of head
- Pulsating or throbbing pain
- Nausea, perhaps with vomiting
- Auras
- Sensitivity to movement, light, and noise
- May exist with tension headache [7].

10-20% of people experience premonitory symptoms for over 48 hrs prior to an episode. An unusual energy spike, yawning, stiff neck, exhaustion, and frequent urination are some of these symptoms. It has been determined which parts of the brain are engaged during the premonitory phase. Most patients also have a postdrome, which includes a bruised feeling in the head, a groaning headache, nausea, exhaustion, and sensitivity to light, noise, and scent, among other things [14].

Table 1: The diagnostic criteria for migraine headaches as formulated by the International Headache Society [11].

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

6. CURRENT THERAPY FOR MIGRAINE HEADACHE

Improving the patient's capacity to function is the main objective of migraine treatment. It is important for providers to assist patients in setting reasonable expectations for what successful treatment will look like (i.e., attacks are unlikely to completely cease) and the time it may take to achieve that end, as finding the best therapy to achieve this goal can be an iterative process for many patients. By carefully considering and understanding patient preferences, healthcare professionals can make sure adherence and treatment continuation [19].

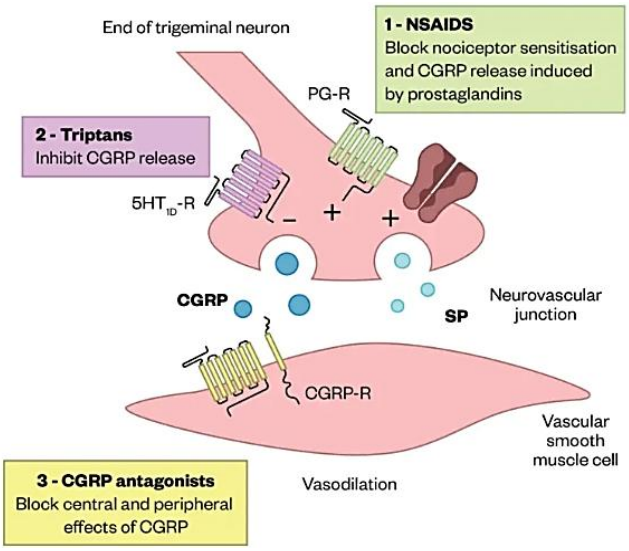

Figure 3: Mechanisms of action of antimigraine treatments used in chronic migraine and emerging treatments in relation to calcitonin gene-related peptide (CGRP)CGRP, calcitonin gene-related peptide; SP, Substance P; PG-R, prostaglandin receptor [20].

6.1 Triptans

The first medications specifically designed to treat migraines were created in the 1990s and are referred to as triptans [10]. The classical vascular hypothesis and the role of serotoninergic neurotransmission, two etiological factors implicated in the pathophysiology of migraines, served as the foundation for the creation of triptans [21]. Sumatriptan, eletriptan, rizatriptan, almotriptan, frovatriptan, naratriptan, and zolmitriptan are the seven that are now accessible [22].

6.1.1 Mode of Action of Triptans:

Triptans are believed to function as anti-migraine medications by activating the presynaptic 5-HT1D receptor, which inhibits dural vasodilation and neurogenic inflammation; activating the vascular 5-HT1B receptors, which causes meningeal, dural cerebral, and pial vasoconstriction; and inhibiting the excitability of trigeminal nuclei cells through 5-HT1B/D activation in the brainstem [23].

6.1.2. Sumatriptan In Migraine:

The first triptan medication to be made clinically available was sumatriptan, which was originally launched in 1991 [23]. The most often prescribed medication among triptans is sumatriptan (ST), which was authorised by the US FDA in 1992 to treat migraine attacks. The strongest antiemetic effect that can alleviate migraine-related nausea is revealed by ST administration. Numerous clinical trials have examined the safety and efficacy of different ST routes, including oral, intranasal, transdermal, subcutaneous, and rectal, and associated formulations are currently in use [24]. The 5-HT1B/1D receptors are the primary site of action for sumatriptan, a highly selective 5-hydroxytryptamine (5-HT) receptor agonist, with much less activity on the 5-HT1A, 5-

HT1E, or 5-HT1F receptors. While 5HT1D receptors are found in neural tissue, vascular 5HT1B receptors are mostly found in the cerebral and dural arteries. Large cerebral and meningeal blood arteries vasoconstrict when these receptors are activated, neurogenic vasodilation is reduced, and pain impulses from second-order neurones are not transmitted as well to the trigeminal nucleus caudalis. By preventing communication between peripheral and central neurones, triptans may hinder the activation of central pathways in the early phases of a migraine episode [25].

6.1.3 Pharmacokinetics:

The oral sumatriptan's bioavailability is 14%. For sumatriptan, the Tmax for plasma concentration following oral treatment is 1.5 hours, the Tmax for subcutaneous injection is 10 minutes, the subcutaneous bioavailability is 96%, and the elimination half-life in plasma is 2 hours [26].

6.1.4 Contraindications:

Due to their vasoconstrictive activity, triptans are not advised for people who have a history of heart or cerebrovascular illness or who are at risk of getting them. In addition to their limited effectiveness, triptans should not be taken by pregnant or nursing women [27]. People with coronary artery disease, coronary artery vasospasm, Wolff-Parkinson-White or other cardiac accessory conduction pathway disorders, a history of stroke, This medication should not be taken by anyone who has a transient ischaemic attack, hemiplegic or basilar migraine, peripheral vascular disease, ischaemic bowel disease, uncontrolled hypertension, concurrent use of MAO-inhibitors or ergotamine derivatives, an allergy to sumatriptan or its metabolites, or severe liver disease that would affect the drug's metabolism. Other licensed triptans with similar contraindications for vascular illnesses include zolmitriptan (1997), rizatriptan (1998), naratriptan (1998), almotriptan (2001), frovatriptan (2001), and eletriptan (2002) [28].

6.2 Ditans:

It became necessary to create a more specialised migraine treatment with no negative effects on the heart or brain. 5-HT1F receptors were thought to be a potential victim for drugs that target neurones (trigeminal pathway) [27].

6.2.1 Lasmiditan:

Lasmiditan is the first of the “ditan” class of medications, which may be an opportunity to fulfill the need for rescue therapies for patients with vascular contraindications. Lasmiditan hemisuccinate’s chemical name is 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl]benzamide hemisuccinate. This compound exhibits a pyridinoyl-piperidine scaffold, which is not found in other anti-migraine rescue therapies and is thought to contribute to its unique properties [28]. The LDT replaces the indole group of triptans by a pyridine-piperidine scaffold, which provides to the structure high affinity for the 5HT1F receptors [29]. When triptan is contraindicated, lasmiditan may be administered preferred. Lasmiditan's effectiveness and tolerability in patients with triptan contraindications are therefore particularly pertinent to clinical practice. Although cardiovascular risk factors were the focus of earlier research, this group is substantially broader and might be less susceptible to adverse events than individuals with clear contraindications [30]. lasmiditan was effective and reasonably well tolerated when used to treat a single acute migraine attack at doses of 200 mg, 100 mg, and 50 mg. By showing that a statistically significant higher proportion of patients in each of the lasmiditan treatment groups were headache pain-free compared to placebo, the study achieved its main goal [31].

6.2.2 Pharmacokinetics of Lasmiditan:

LDT exhibits a quick onset of action, rapid absorption, and good oral bioavailability. Within two hours, the plasma reaches its peak, and half of the distribution is linked to proteins. LDT is metabolised by noncytochromes P450 in a hepatic and nonhepatic manner. Since LDT is thought to enhance the effects of the P-glycoprotein (MDR1) efflux transporter, it interacts with often used migraine medications including amitriptyline and eletriptan. There is a noticeable decrease in heart rate when propranolol is taken with it. When taken with LDT, other drugs such as apixaban, amiodarone, ciprofloxacin, and pantoprazole also require constant monitoring. Coadministration of monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors can also increase the risk of serotonin syndrome.

6.2.3 Adverse effects:

The only side effect that affects more than 10% of people is dizziness. Paraesthesia, sedation, exhaustion, nausea, vomiting, and muscle weakness will affect 1% to 10% of the population. A considerable section of the economically active population is impacted by the FDA's advice that users should refrain from using machinery or driving for at least eight hours after taking the medicine [29].

6.3 Gepants:

6.3.1 Mode of Action:

Gepants are CGRP receptor antagonists that are tiny molecules. They work by attaching themselves to CGRP receptors and preventing CGRPs and their receptors from interacting. The activation of these receptors and the ensuing series of biochemical reactions that raise the sensitivity of pain-sensing nerve fibres, widen blood vessels, and encourage the release of inflammatory mediators are stopped by this mechanism. Headache and other migraine symptoms are exacerbated by these occurrences [33].

6.3.2 Ubrogepant:

In December 2019, the FDA approved uberogepant for the acute treatment of migraines [33]. Uberogepant has been approved at doses of 50 and 100 mg. Additionally, preliminary data supports the effectiveness of the non-oral gepant zavegepant nasal spray. Gepants are a good choice for treating this problem since, crucially, they don't appear

to cause medication overuse headache. It has a high effectiveness rate when taken in several doses throughout the onslaught. Although the low side effect profile of gepants is alluring, prudence is warranted in the early stages of practical application [3].

6.3.3 Pharmacokinetics:

In vitro, 87% of plasma proteins bind. The CYP3A4 enzyme in the liver metabolises it. Two glucuronide conjugate-based metabolites of ubergepant are pharmacologically inactive and 6000 times less powerful than the original gepant. The elimination half-life is five to seven hours, and the elimination pathway is essentially biliary/fecal. Monkey studies have shown that ubrogepant has a low CGRP receptor occupancy and a cerebrospinal fluid plasma ratio of 0.0334, which indicates that it passes the hemato-encephalic barrier**.**

6.4 Calcitonin Gene-Related Peptide (CGRP)-Related Mechanisms and Therapies:

The 37-amino acid neuropeptide known as calcitonin gene-related peptide (CGRP) is highly conserved throughout species. The trigeminovascular system has a large number of peripheral and centrally located CGRP-expressing sensory nerve fibres and CGRP receptors. Along with amylin, adrenomedullin, and intermedin/adrenomedullin, CGRP belongs to the structurally similar peptide family known as calcitonin (CT) [35].

The trigeminal ganglion contains the sensory neuropeptide CGRP, and migraine discomfort is directly correlated with the amount of this neuropeptide in central venous circulation. According to pathophysiology, CGRP is a strong vasodilator. Through the trigeminal nerve's A fibre sensory neurones, which are involved in pain perception, and satellite glial cells, which regulate pain sensitivity and transmission when a pain signal is begun, it plays a crucial part in the sensory signalling pathway both centrally and peripherally. The CGRP receptor, amylin receptors, calcitonin receptors, and adrenomedullin receptors are the four receptor types that CGRP interacts with. Two receptors the CGRP receptor and the amylin receptor, or AMY1 bind to CGRP with a notably high affinity. The peptide and its high-affinity receptors are specific targets for medication in the treatment of migraine headaches, as testing has shown higher levels of serum CGRP during migraine attacks [36]. For the first time since the triptan period, well-tolerated and specifically targeted migraine therapies are becoming available due to the development of innovative targeted medicines that act on the CGRP pathway. Early research has demonstrated that taking them during PS can effectively avoid headaches [37]. Investigating the central and peripheral mechanisms of CGRP receptor antagonism was the study's goal. Olcegepant decreased the expression of CGRP in the trigeminal nucleus and proinflammatory markers such cytokines, microRNA-132, and TRPA1, the investigators reported, hence reducing the prevalence of trigeminal hyperalgesia. Antagonism of the CGRP receptor plays a significant role in both the central and peripheral processes of chronic migraine. The aforementioned study may aid in the creation of innovative therapeutic approaches for chronic migraine, which could improve patient outcomes and quality of life [38]. When the trigeminal nerve is activated, its peripheral projections produce neurotransmitters, such as calcitonin gene-related peptide (CGRP), which cause vasodilation and alter nociceptive transmission [39].

6.5 Ergot alkaloids:

The use of ergots dates back to the 1920s. At adrenergic, dopaminergic, and serotonergic receptors, they function as agonists. They should be taken as soon as the headache starts, much like the triptans. Clinical research has shown that dihydroergotamine (DHE) can prevent repeated headaches by acting late in the migraine episode and for a considerable amount of time. It can be purchased as an injectable or nasal spray [40]. Cluster headache episodes and migraine headaches with or without aura can both be acutely treated with dihydroergotamine (DHE). The 5-HT1Dα and 5-HT1Dβ receptors are highly affinitized for DHE [25]. The ergoline ring is a component of the chemical structure of all ergot alkaloids. Ergotamine's unsaturated link is reduced to create DHE, a semisynthetic, hydrogenated ergot alkaloid. An ergot derivative with increased alpha adrenergic antagonist action and decreased vasoconstrictor activity is the result of this chemical alteration [41].

6.5.1 Mode of Action:

All ergot alkaloids bind to dopamine and α-adrenoceptors and are non-specific 5-HT1 receptor agonists. Initially, it was believed that the pharmacological impact of ergot alkaloids of greatest importance in migraine was arterial vasoconstriction by binding to 5-HT1B receptors and α-adrenoceptors, even if their primary action is still unknown. However, they also have a central effect by activating trigeminal nerve terminal 5-HT1B, 5-HT1D, and 5-HT1F receptors, which inhibits the production of vasoactive peptides and prevents migraine vasodilatation [42]. In the 18th and 19th centuries, ergot alkaloids were most commonly used to alleviate headaches and manage postpartum haemorrhage [43]. Large-scale poisonings from eating tainted grains have historically characterised human interactions with ergot alkaloids. Because of advancements in crop management, grain screening and cleaning, and the regulation of safe levels in food and feed, human ergot poisoning incidents are becoming less frequent. This can still be a problem in some parts of the world, though, and ergot alkaloids potential as a medication is still being studied [43].

6.5.2 Adverse effect:

The most frequent side effects of DHE are nausea, dizziness, and vasoconstriction, indicating that DHE does, in fact, act on adrenergic, muscarinic, and dopaminergic receptors [29]. Because it is less expensive, ergotamine tartrate is used more often and excessively in other nations than it was in the United States prior to the advent of triptans. It can be compounded as a suppository or administered as a tablet or sublingual tablet [40].

6.6 NSAIDS:

Nonsteroidal anti-inflammatory medications (NSAIDs) have been one of the most popular treatments in the world for more than a century. Many inflammatory and pain diseases, including migraine, can be treated with both prescription and over-the-counter NSAID formulations. NSAIDs can offer analgesia at any point during a migraine episode and work in both the central and peripheral nerve systems, which sets them apart from other migraine medications. Nonprescription NSAIDs are the only treatment used by up to half of all migraineurs, and they are frequently taken in inadequate amounts [33].

6.6.1 Mechanism of action of NSAIDs:

NSAIDs, including naproxen and diclofenac, work by inhibiting the cyclooxygenase enzyme to provide their analgesic effects. The production of prostaglandins, which contribute to the pain and inflammation observed in numerous rheumatologic disorders, depends on the COX enzymes. The expression and function of the two isoforms of the enzyme, COX-1 and COX-2, vary. The constitutively expressed COX-1 isoform produces prostaglandins (PG), which are essential for regular physiological processes like vascular maintenance and gastrointestinal mucosal protection. Inducible, the other isoform, COX-2, contributes to pain and inflammation in specific disease conditions. NSAIDs reduce inflammation and pain by blocking the formation of prostaglandins by blocking the COX enzyme [44].

NSAID use, however, has been linked to a higher risk of adverse gastrointestinal (GI) events, which can occasionally be quite serious. In a large study (N = 24,081) comparing them for long-term use for osteoarthritis and rheumatoid arthritis, celecoxib, a selective COX-2 inhibitor that produces analgesia similar to other NSAIDs, demonstrated a significantly lower risk of GI events than naproxen (P =0.01) or ibuprofen (P =0.002), as well as a significantly lower risk of renal events than ibuprofen (P =0.004). Celecoxib is used to relieve acute pain in people with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and primary dysmenorrhea. Celecoxib (Celebrex®; Pfizer Inc., New York, NY, USA) has been evaluated as an acute migraine treatment in the past [45].

6.6.2 Pharmacokinetics of Celecoxib:

When taken during a fast, celecoxib oral capsules (Celebrex, Pfizer Inc., USA) reach peak plasma concentrations (Cmax) in around 3 hours. Within the therapeutic range, celecoxib is largely protein bound (*97%), and its apparent volume of distribution (Vd/F) at steady state is around 400 L, indicating widespread tissue distribution. Celecoxib is mostly eliminated through the cytochrome P450 (CYP)-2C9 metabolic route; very little of the drug is found unaltered in faeces or urine. About 500 millilitres per minute is the apparent plasma clearance (Cl/F). Its low solubility seems to prolong the absorption of celecoxib, causing variations in terminal half-life (t1/2) assessments and an effective half-life of around 11 hours when fasting. Additionally, delayed oral absorption reduces the beginning of action and obstructs quick pain alleviation, which is a key treatment objective of acute migraine therapy [46] . The new liquid form of celecoxib, ELYXYB (celecoxib oral solution, 25 mg/mL; formerly known as DFN-15), was authorised in May 2020 for the immediate treatment of adult migraines with or without aura. Compared to other celecoxib capsule formulations, it has a shorter shown Tmax (median 0.7 hours) [47].

6.7 Analgesics :

Acetaminophen, sometimes referred to as paracetamol in the EU, and its combinations with other drugs are examples of analgesics. For many years, paracetamol has been used extensively around the world as an all-purpose analgesic and antipyretic [48].

As an adjuvant, caffeine is used to relieve headaches and discomfort. In certain clinical pain circumstances, such as postdural puncture headache, caffeine by itself exhibits analgesic effects. According to a 2014 Cochrane analysis, analgesics (such as aspirin, ibuprofen, or paracetamol) with and without 100–130 mg of caffeine were found to have a considerably higher response rate in cases of acute pain. APC outperformed aspirin and paracetamol in a head-to-head study for treating migraine and acute tension-type headaches [49].

In the emergency department (ED), children with migraine headaches are frequently treated with ketorolac, an analgesic. The intravenous (IV) method is commonly used to provide ketorolac, a nonsteroidal anti-inflammatory medicine (NSAID). When compared to other routes that do not require IV access, administering analgesics via the IV route may take longer. Ketorolac can be administered by the intranasal (IN) route, which eliminates the need for an IV or needlestick [50].

7. CONTRAINDICATIONS

Liver impairment and a prior history of MOH are contraindications. To avoid MOH, paracetamol should not be taken for more than 14 days in a month, or for more than 9 days if taken with another drug. Due to the possibility of liver toxicity, 3,000 mg of paracetamol should not be used daily [49]. Chronic headaches can be treated with aspirin alone or in combination. Because aspirin inhibits the COX enzymes, thromboxane production is hampered. As an antiplatelet medication, aspirin also increases the risk of bleeding. Both oral and intravenous methods can be used to give aspirin [13].

CONCLUSION

Managing migraines requires a multifaceted approach, considering individual patient needs, triggers, and responses to various therapies. By understanding the complexities of migraine pathophysiology and exploring new treatment avenues, healthcare professionals can improve patient outcomes and quality of life. The development of novel therapies, such as CGRP receptor antagonists, offers promising prospects for more effective migraine management. As research continues to unravel the intricacies of this debilitating condition, we can expect to

see more targeted and efficient treatments emerge, ultimately enhancing the lives of those affected by migraines.

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