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Review

Advancing Migraine Management: Insights into Pathophysiology and Innovative Treatment Modalities with Nanoformulation

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Abstract

Migraine is a prevalent neurological disorder characterized by recurrent severe headaches, often accompanied by nausea and sensitivity to light and sound. Affecting approximately one billion individuals globally. This complex condition encompasses various types of migraines, including those with aura and chronic forms, significantly impacting daily functioning and quality of life. The pathophysiology of migraines is primarily attributable to the activation of the trigeminovascular system and the release of calcitonin gene-related peptide (CGRP), resulting in neurogenic inflammation and heightened pain sensitivity. Factors contributing to migraines include genetic predispositions and environmental triggers, such as stress and hormonal changes. Treatment modalities encompass acute interventions like NSAIDs and triptans, and preventive strategies involving beta-blockers and CGRP monoclonal antibodies, complemented by lifestyle modifications and behavioural therapies. Emerging Nanoformulations are revolutionizing migraine treatment by enhancing bioavailability and crossing the blood-brain barrier and enabling targeted drug delivery with minimal systemic side effects. Compared to conventional treatments, they offer several advantages, including improved drug absorption, therapeutic efficacy, and sustained release. As personalized medicine evolves, integrating genetic insights and digital health tools, the future of migraine treatment aims at more effective, tailored interventions, improving the overall management of this debilitating condition and enriching patient quality of life.

Keywords: Pathophysiology, CGRP (Calcitonin Gene-Related Peptide), Sensitization, Treatment Modalities, Nanoformulation, Migraine Management.

INTRODUCTION

Migraine is a common episodic neurological illness with a complicated etiology characterized by recurring bouts of throbbing and unilateral, often severe headaches, as well as accompanying symptoms such as

nausea, phonophobia, and photophobia. Migraines affect roughly 1 billion people worldwide, making them the second biggest cause of disability and the main cause of disability in people under the age of 50. It is not a single, homogeneous disorder, but rather a collection of symptoms. The International Headache Society (IHS) developed the International Classification of Headache Disorders (ICHD, 2nd edition), (Given in Fig. No 1)which provides a hierarchical classification system and is widely regarded as the most important guideline for clinicians and others involved in the diagnosis and treatment of headache disorders [1,2].

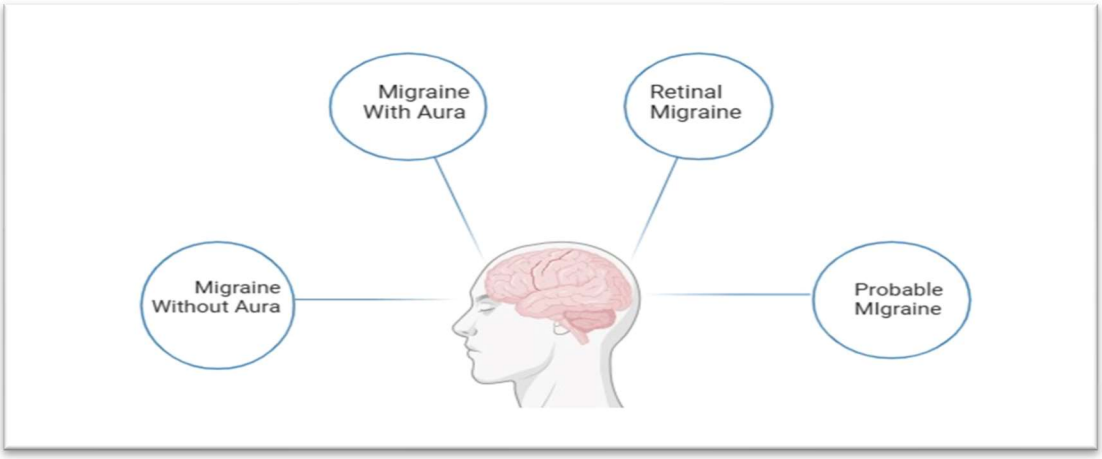

Fig 1: International Classification of Headache Disorders (ICHD, 2nd edition)

Headache disorders are divided into two types. Secondary headache problems have a clear underlying cause, such as an infection, brain tumour, or stroke. Primary headache diseases, on the other hand, do not have a defined cause. Tension-type headaches are the most typically reported in population research, but migraines are the most common reason individuals seek medical attention for headaches. The three most prevalent kinds of migraine are migraine with aura, migraine without aura, and probable migraine (PM) [3]. In one-third of patients, the headache is preceded by transitory neurological symptoms, which are most commonly visual but may impact other senses including speech. [Migraine with aura (MA)] [4].

The majority of migraine sufferers experience "episodic migraine," which lasts fewer than 15 days per month. A subset of migraine sufferers experience "chronic migraine," which is defined as at least 15 days of headache per month, including at least eight days with symptoms similar to fully formed migraine attacks. Chronic migraine often develops gradually over months or years, a process known as "migraine transformation"[5]. Migraine and tension-type headache (TTH) are two frequent main headache disorders that impact up to 80% of the global population (1). Migraine and TTH headaches are typically classed as episodic (<15 headache days per month) or chronic (15 headache days per month) (2). Primary chronic headaches (including chronic migraine (CM) and chronic TTH) are prevalent, affecting 3% to 4% of the general population (3-8), with CM in particular posing a considerable health burden on people, their families, and society [6].

Phases of a migraine attack

The phases of a migraine attack can be separated into the following categories based on their temporal relationship to the headache: premonitory (prior to the headache), aura (prior to or concurrent with the headache), headache, and postdrome (after the headache has resolved). While this is a useful way to describe a migraine attack, the phases may overlap and vary [7]. Although the phenotypic of primary headaches can vary greatly, they have a significant pathophysiology; it is thought that the activation of neural circuits within the trigeminovascular system mediates the headache pain [8].

Pathophysiology of migraine

Numerous ideas, such as the vascular theory, the neural theory, and the trigeminovascular theory, have been put up to explain the pathophysiology of migraines [9].

Neurovascular theory

According to the neurovascular theory, migraines are caused by the trigeminovascular system becoming activated, which results in a dynamic interplay between vascular and neurological components. A key aspect of this mechanism is the release of calcitonin gene-related peptide (CGRP) from trigeminal nerve endings. This release leads to vasodilation, plasma protein leakage, and neurogenic inflammation in the meninges, contributing to migraine symptoms and progression. The trigeminal nerve and CGRP thus play critical roles in initiating and sustaining migraine pathophysiology [10,11]. Consistently elevated CGRP levels during migraine attacks have

been observed to decrease to normal levels following effective treatment. This pattern underscores the pivotal role of CGRP in the mechanisms underlying migraine pathology (Shown in Fig. No. 2) [12 -14].

Activation of the trigeminal nerve promotes the sensitization of nociceptive pathways in the brainstem and thalamus, intensifying the perception of pain during migraine episodes [15-17]. Cortical spreading depression (CSD), characterized by a wave of neuronal and glial depolarization followed by cortical activity suppression, is believed to initiate the release of vasoactive substances such as CGRP. This mechanism establishes a connection between CSD and the development of the aura and subsequent headache phases in migraine [18-20]. Neuroimaging studies offer further support for the neurovascular hypothesis, showing increased activity in brainstem regions, such as the periaqueductal grey and dorsal pons, during migraine episodes. These findings highlight the involvement of central nervous system structures in the pathophysiology of migraines [21-23]. Additionally, the successful development and clinical use of CGRP receptor antagonists and monoclonal antibodies targeting CGRP for both acute and preventive migraine treatments have further reinforced the essential role of CGRP in migraine pathophysiology. These therapies have demonstrated significant effectiveness in reducing migraine frequency and severity, solidifying CGRP's central involvement in the condition [24-26]. These therapies not only inhibit the action of CGRP but also help to decrease the frequency and intensity of migraine attacks, providing significant clinical improvements for patients [27- 29].

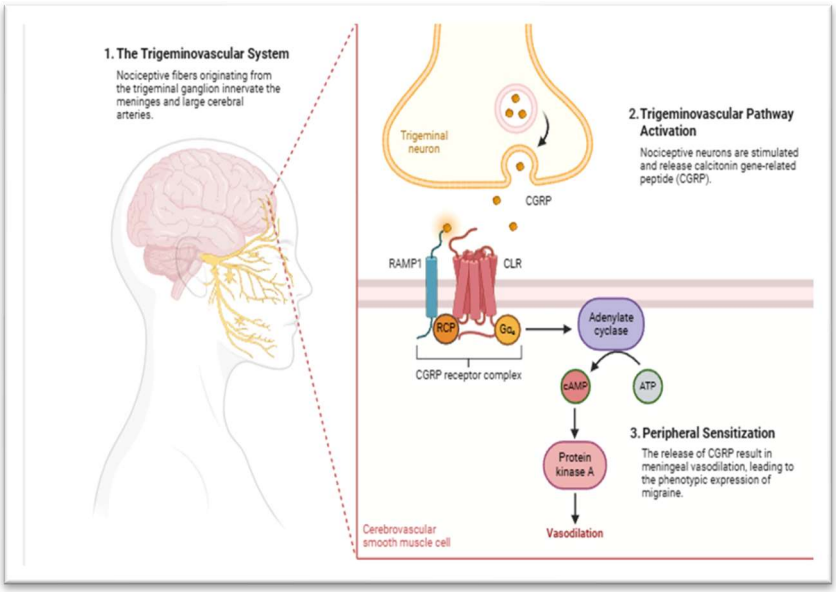

Fig 2: The Role of CGRP and the Trigeminal System in Migraine Pathophysiology

Central and Peripheral Sensitization in Migraine Pain Perception

Central and peripheral sensitization are key factors in the increased pain perception seen in migraines. Peripheral sensitization occurs when nociceptors in the trigeminal ganglion become overly responsive to stimuli due to the release of inflammatory mediators like calcitonin gene-related peptide (CGRP) and substance P. (Shown in Fig. No.3) This process amplifies pain signalling, resulting in throbbing headache pain and allodynia, where even non-painful stimuli provoke discomfort. These changes underline the role of peripheral mechanisms in migraine pathophysiology [30-33]. Central sensitization involves heightened excitability of central neurons located in the brainstem, thalamus, and cortical regions. Prolonged nociceptive input from peripheral pathways drives sustained central activation, intensifying pain perception and prolonging symptoms such as photophobia, phonophobia, and scalp tenderness. Further strengthening central pain pathways and adding to the duration and intensity of migraine symptoms is cortical spreading depression (CSD), a wave of neuronal and glial depolarization linked to migraine aura that triggers the release of neuropeptides and excitatory mediators [34-38].

Neuroimaging studies consistently indicate heightened activity in the dorsal pons and hypothalamus during migraine episodes, underscoring the role of central mechanisms in migraine pathophysiology. These brain regions are integral to processing nociceptive input and modulating pain pathways, contributing to the initiation and propagation of migraine symptoms [39-41]. In both peripheral and central sensitization pathways, maladaptive changes are closely associated with the transition from episodic to chronic migraine. These modifications increase the frequency and severity of migraine episodes, which prolongs the discomfort and other related symptoms over time [42]. The efficacy of CGRP inhibitors and other therapies that target sensitization pathways underscores their significance in migraine treatment. By disrupting these pathways, these treatments

effectively decrease the intensity and frequency of migraine attacks, providing strong clinical evidence for the function of both peripheral and central sensitization in migraine pathophysiology [43,44].

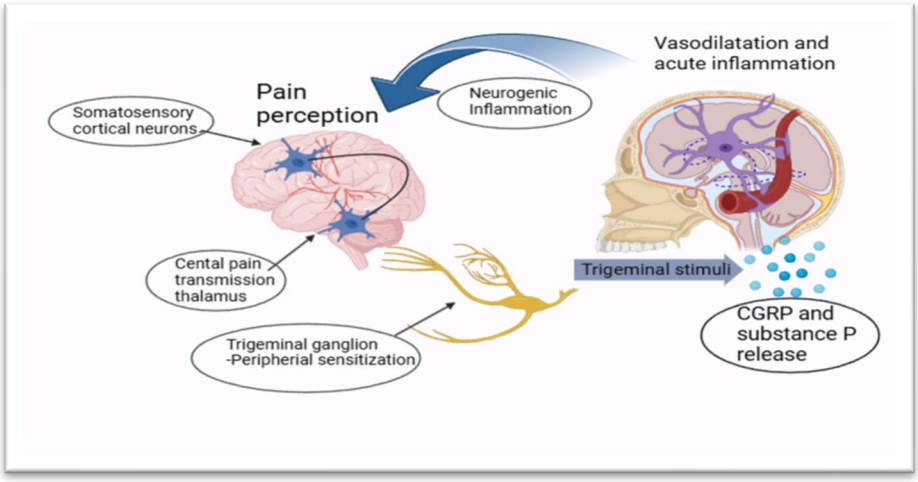

Fig 3: Mechanism of migraine development – pain perception

Genetic and Environmental Factors in Migraine

Migraine is a complex condition caused by both genetic and environmental causes. Familial aggregation studies reveal a substantial genetic component, with a greater prevalence of migraines in those with a family history [45,46]. Research has discovered numerous genes associated with migraine susceptibility, including CACNA1A, TRPM8, and MTHFR, which affects ion channel function, vascular control, and neurotransmitter pathways [47,48]. These genetic variables affect neuronal excitability and vascular function, which contribute to an individual's propensity to migraines (Shown in Fig.No.4) [49]. Environmental stimuli are also significant in the development of migraine attacks. Stress is one of the most widely reported triggers. Both acute and chronic stress activate brain sensitisation pathways, which lower the threshold for pain perception [50,51]. Due to hormonal fluctuations, migraines are more likely in women than in men; variations in oestrogen levels have been shown to precipitate attacks, notably during menstruation, pregnancy, and menopause [52]. Migraine attacks are also significantly triggered by sleep disruptions, such as inadequate sleep or irregular sleep patterns [53].

Patients often attribute migraine attacks to dietary triggers such alcohol, coffee, chocolate, and foods containing MSG, in addition to hormonal and sleep-related issues [54,55]. For many people with migraines, environmental elements including bright lights, loud noises, and weather changes especially those involving variations in barometric pressure are significant physical triggers [56]. Furthermore, the interaction between genetic susceptibility and environmental factors is essential in understanding the progression of migraines. While genetic factors may lower an individual's threshold for developing migraines, environmental triggers can initiate the onset of symptoms, highlighting the multifactorial nature of the disorder [57,58]. Studies on migraines have shown that both hereditary and environmental factors have a substantial impact on the risk, frequency, and severity of migraine attacks [59].

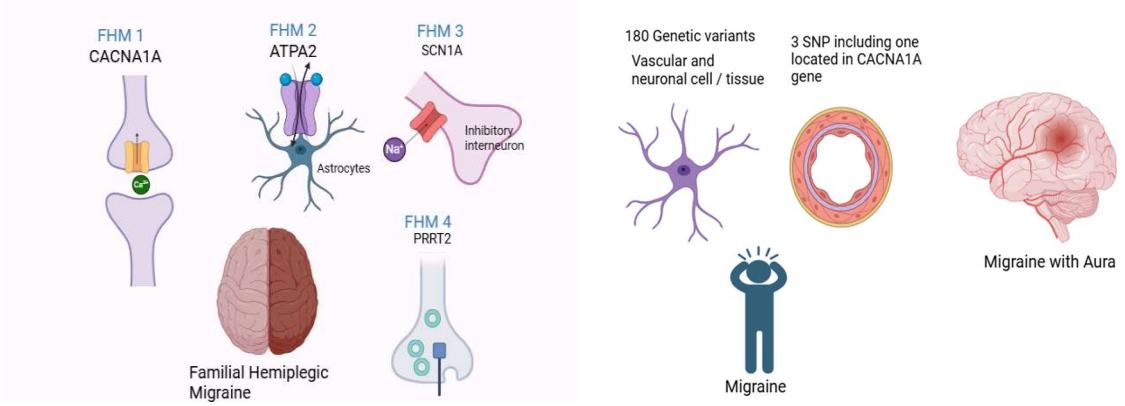

Fig 4: Genetics of migraine

Role of the Brainstem and Cortical Spreading Depression (CSD) in Migraine

The pathogenesis of migraines, especially those with aura, is significantly influenced by cortical spreading depression (CSD). The visual abnormalities frequently seen during aura are associated with CSD, which is characterised by a slow-moving wave of neuronal and glial depolarisation followed by cortical suppression. Vasoactive chemicals such as nitric oxide and calcitonin gene-related peptide (CGRP) are released as a result of this event, activating the trigeminovascular system and causing headaches (Given in Fig.No.5) [60,61]. Recent research shows that CSD increases the permeability of the blood-brain barrier, which promotes neurogenic inflammation and central sensitisation, both of which increase nociceptive signalling. Functional neuroimaging studies have shown increased activity in the brainstem during migraine episodes, specifically in the dorsal pons and periaqueductal grey, which are important in modifying pain processing during migraine attacks [62]. These regions play a part in migraineurs' reported increased sensitivity to light and sound, among other sensory stimuli [63].

Furthermore, it is believed that migraine attacks are sustained by the connection between CSD and the brainstem. Signalling routes produced by CSD can alter brainstem centre activity, enhancing nociceptive input and extending the duration of migraines. Knowing these mechanisms makes it easier to identify possible treatment targets, including CGRP inhibitors, which have been found to be effective in reducing headache and aura symptoms by interfering with pathways linked to CSD [64].

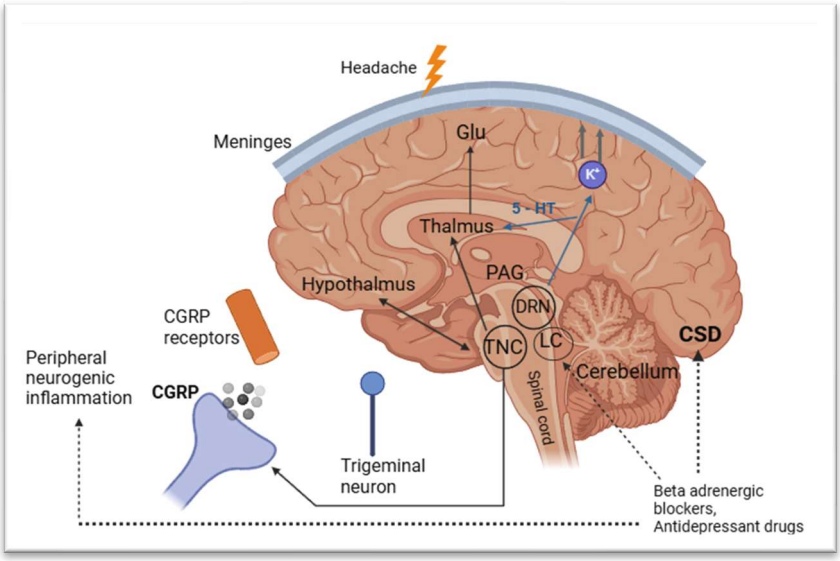

Fig 5: Cortical spreading depression as a target for antimigraine agents

Treatment Modalities

For the sake of simplicity, this evaluation adheres to the historical division of migraine management into acute and preventive treatments. However, it is increasingly clear that this binary principle may actually be outdated [65].

Acute Treatment Modalities

Analgesics and NSAIDs

Nonsteroidal anti-inflammatory medicines (NSAIDs) and over-the-counter (OTC) analgesics are commonly used for severe migraine attacks, especially those that are mild to moderate. Aspirin, ibuprofen, and acetaminophen are frequently advised, and combination formulations (such as acetaminophen-aspirin-caffeine) offer increased efficacy because of their synergistic effects. By preventing the creation of prostaglandins, these medications lessen pain and inflammation [66,67]. However, prolonged use of acetaminophen might result in hepatotoxicity or gastrointestinal discomfort, as well as medication-overuse headache (MOH). Adjunctive therapy may be necessary because NSAIDs may not address related symptoms like nausea or photophobia. While optimal dose lowers dangers, early delivery at the onset of headaches boosts efficacy [68-70].

Triptans

For moderate to severe migraines, triptans, such sumatriptan and rizatriptan, are quite beneficial. As agonists of the serotonin (5-HT1B/1D) receptor, they suppress trigeminal nerve activation, promote vasoconstriction of dilated cranial blood vessels, and decrease the release of pro-inflammatory neuropeptides such as CGRP. Triptans can reduce headache, nausea, and light and sound sensitivity, and they work best when taken early in a migraine attack [71]. Triptans do have certain drawbacks, though. Because of their vasoconstrictive

characteristics, they should not be used in patients who have cardiovascular disorders (4-6). Furthermore, they might not work for migraines that show atypically or have a prolonged aura. For some people, side symptoms like exhaustion, light headedness, and tightness in the chest may restrict tolerability. Patients who do not respond well to monotherapy may benefit from combination therapy (e.g., triptans with NSAIDs) [72].

Ergots

Older migraine remedies include ergot alkaloids, such as ergotamine and dihydroergotamine (DHE). By acting as agonists of the serotonin (5-HT1B/1D) receptor, these medications significantly reduce migraine symptoms by causing cranial vasoconstriction and neurogenic inflammation [73]. However, because of adverse effects like nausea, vasospasm, and the possibility of medication-overuse headache, their use has drastically decreased. Pregnant women and those with cardiovascular disease should not take them. DHE is still sometimes used to treat refractory migraines because it is thought to be safer than ergotamine [74].

New Acute Treatments

Patients who are refractory to conventional treatments now have options thanks to emerging medications for acute migraine that concentrate on novel mechanisms of action. Trigeminal nociceptive signalling is inhibited by Lasmiditan, a selective 5-HT1F receptor agonist, which lessens migraine discomfort without constricting blood vessels. Although it may cause drowsiness and dizziness, it works well for people whose cardiovascular systems are contraindicated for triptans [75,76].

By blocking the function of calcitonin gene-related peptide, CGRP receptor antagonists like Ubrogepant and Rimegepant treat pain and its related symptoms. Compared to conventional solutions, these have fewer adverse effects and are well-tolerated [77].

Preventive Treatments

Beta-blockers: The most popular class of medications for treating preventative migraines are β-blockers, which are roughly 50% successful in reducing the incidence of attacks by more than 50%. Metoprolol and propranolol are examples of β-blockers that seem to work well because they penetrate the blood-brain barrier, take advantage of their lipid solubility, and alter neuronal excitability [78].

Antidepressants: Antidepressants, especially tricyclic antidepressants (TCAs), were initially found to be effective in preventing migraines. Two antidepressants, amitriptyline and venlafaxine, have been highly rated in guidelines for the prevention of migraine. Tricyclic antidepressants inhibit serotonin and norepinephrine absorption while also exhibiting anticholinergic and antihistaminergic properties [79].

Antiepileptics: Antiepileptic medications (AEDs) show promise for preventing migraines and other types of headaches. Published guidelines recommend valproate as a first-line therapy for migraine prophylaxis. Its method of action in migraine is unclear, however it could be through a variety of mechanisms, including enhanced GABA-mediated neurotransmission, attenuation of low-threshold T-type calcium channels, blockage of voltage-dependent sodium channels, and attenuation of plasma extravasation [80].

CGRP Monoclonal Antibodies

The trigeminal nerve's most abundant neuropeptide, CGRP, has been linked to migraine aetiology. CGRP does not directly affect dural nociceptors, but rather interacts with neurones, astrocytes, immune cells, and blood vessels in the meninges. It causes vasodilation, plasma extravasation, neurogenic inflammation, SGC activation, and mast cell degranulation, leading to peripheral and central sensitisation [81].

OnabotulinumtoxinA

The FDA has approved OnabotulinumtoxinA (Botox) for the treatment of persistent migraines, defined as headaches occurring 15 or more days per month, with at least eight of those being migraines. Botox inhibits the release of neurotransmitters such as acetylcholine, which reduces the activation of pain pathways in peripheral and central sensitisation [82].

Non-Pharmacological Treatments

Lifestyle Modifications

Lifestyle changes are essential in non-pharmacological migraine management. Avoiding food irritants like caffeine, alcohol, and artificial sweeteners can help reduce migraine frequency Consistent sleep schedules serve to regulate brain function and lower the risk of attacks induced by sleep deprivation or abnormalities. Stress management approaches such as mindfulness meditation, yoga, and biofeedback reduce cortisol levels, which can worsen migraines. Combining these measures with pharmaceutical interventions frequently improves treatment efficacy and quality of life for migraine sufferers [83].

Behavioural Therapies: Cognitive-Behavioural Therapy (CBT) and Biofeedback. Behavioural therapies such as CBT and biofeedback are excellent non-pharmacological migraine treatments. CBT aims to change maladaptive thought patterns and behaviours that can increase migraine symptoms, such as stress-related triggers and

inadequate coping techniques. CBT has been shown in studies to considerably reduce migraine frequency while also improving patient quality of life [84]. Biofeedback, which trains people to manage physiological processes such as muscular tension and skin temperature, has been shown to reduce the intensity and frequency of headaches. It works particularly well when paired with relaxation techniques [85].

Devices: Include neuromodulation devices like transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS). Neuromodulation devices, such as transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS), have shown promise as non-pharmacological migraine therapies. TMS works by sending magnetic pulses to specific brain regions, modifying cortical excitability, hence preventing or treating migraine attacks. According to studies, TMS decreases migraine frequency and severity while causing little side effects. Similarly, VNS, which involves stimulating the vagus nerve to affect brain activity, has been shown to reduce the frequency of chronic migraines while improving overall migraine-related impairment [86].

Emerging Therapies and Future Direction

New mechanisms of action and enhanced drug delivery techniques are the main goals of emerging migraine treatments. Small-molecule CGRP receptor antagonists known as gepants, including Rimegepant and Atogepant, offer oral substitutes with few adverse effects and exhibit promise in both acute and preventative contexts [87]. For patients for whom triptans are contraindicated due to cardiovascular concerns, Lasmiditan, a selective 5-HT1F receptor agonist, offers an alternative [88]. CGRP monoclonal antibodies with prolonged efficacy that target preventive care are another example of cutting-edge research. For chronic patients, neuromodulation treatments such as combination transcranial stimulation methods and non-invasive vagus nerve stimulation (nVNS) are being optimised. Furthermore, personalised medicine techniques and gene-editing technologies like CRISPR/Cas9 have the potential to completely transform future therapy paradigms [89,90].

Marketed Formulations available for migraine

Migraine treatments are classified into two categories: acute (abortive) therapies for pain relief during an attack and preventive therapies for reducing attack frequency. A detailed look of the marketed formulations is provided below, including brand names, dosage forms, and critical features. (given in Table No. 1)

Table 1: Marketed formulation for migraine

Sr. No.	Drug	Conventional Formulation Type	Brand Names	Limitations	Ref.
1.	**Sumatriptan** Triptan (5-HT1 Agonist)	Oral tablets, Nasal spray, Subcutaneous injection	Imitrex, Alsuma, Imigran	• vasoconstriction risk • Potential for medication overuse headache (MOH). • Common side effects: chest tightness, dizziness, fatigue.	[91]
2.	**Zolmitriptan** Triptan (5-HT1 Agonist)	Oral tablets, Nasal spray	Zomig, Zomig ZMT	• Side effects: nausea, dizziness, chest pressure. • Less effective for severe migraine attacks.	[92]
3.	**Naproxen** NSAID	Oral tablets, Oral suspension	Aleve, Naprosyn, Anaprox	• GI risks: ulcers, bleeding with chronic use. • Less effective for severe attacks compared to triptans.	[93]
4.	**Dihydroergotamine (DHE)** Ergot Alkaloid	Nasal spray, Injectable form	Migranal, DHE nasal	• Risk of nausea and vomiting. Contraindicated in	[94]

			spray, DHE injection	cardiovascular disease (vasoconstriction risk). • Drug interactions with triptans.	
5.	**Botulinum Toxin** Neurotoxin (Preventive)	Injectable form	Botox	• Side effects: muscle weakness, fatigue. • Requires repeated injections, which can be painful.	[95]
6.	**Propranolol** Beta-blocker (Preventive therapy)	Oral Tablets	Inderal, InnoPran	• Side effects: fatigue, dizziness, hypotension • May be contraindicated in asthma or certain heart conditions.	[96]
7.	**Erenumab** CGRP Receptor Antagonist (Preventive)	Subcutaneous injection	Aimovig	• Injection site reactions • High cost. • Long-term efficacy and safety data are still under evaluation.	[97]

Comparison of sales and patient numbers by route of administration for treatment of migraine (Shown in Fig.No.6)

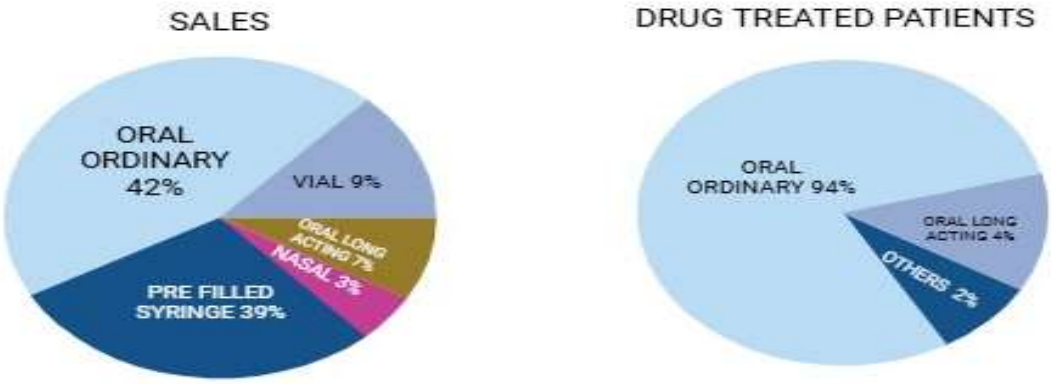

Fig 6. Comparison of sales and patient numbers by route of administration for treatment of migraine

Challenges, Gaps and Personalised medicine in Migraine Treatment

Treating migraine is challenging due to its variability, complex triggers, and multifactorial nature. Traditional treatments, such as triptans, NSAIDs, and preventative drugs, frequently have poor tolerability, limited effectiveness, or a high risk of medication overuse headaches (MOH). New therapies, such CGRP antagonists, show promise but are still expensive and difficult to obtain. By customizing therapies according to clinical, genetic, and environmental aspects, personalized medicine offers a solution. Predicting therapy responses is aided by pharmacogenomics and genetic information, such as variations in the CACNA1A and TRPM8 genes. Digital tools and biomarkers such as CGRP levels allow for real-time tracking and personalized therapeutic modifications. Although personalized medicine has the potential to enhance outcomes, there are still obstacles to its widespread adoption, such as high costs and the need for additional research. [98-101]

Nano-formulation for treating Migraine

Nanoformulations are revolutionizing migraine therapy by enhancing drug delivery, optimizing efficacy, and minimizing side effects. By employing nanotechnology, these formulations address the limitations of conventional treatments, such as poor bioavailability, short half-life, and inadequate blood-brain barrier (BBB) penetration. Common types of nanoformulations for migraine. (Given in Table No. 2)

Table 2: Nano-formulation for Migraine

Sr. No.	Name of Carrier	Route of Administration	In-Vivo/In - Vitro Results	Mechanism of Action	Therapeu-tic Applicati-ons	Ref.
1.	**Cubosomes**	Intranasal	Shown prolonged drug release and improved drug solubility enhanced olfactory pathway targeting of the brain.	Enhanced solubility of poorly soluble medications, leading to a quicker onset of action and increased effectiveness of treatment.	Rapid alleviation of severe headaches and avoidance of recurrent migraine episodes.	[102]
2.	**Lipid nanoparticles**	Intranasal	Increased medication absorption, fewer systemic side effects, and longer retention in brain tissues.	Enhances therapeutic benefits by delivering medications straight to the brain, avoiding systemic circulation.	Faster onset of action and effective management of acute migraine discomfort.	[103]
3.	**Polymeric nanoparticles**	Oral	In vitro experiments confirmed regulated drug release with increased bioavailability, while in vivo tests demonstrated prolonged efficacy.	Slow degradation enables long-term drug release and sustains therapeutic levels.	beneficial for the preventative management of both acute and chronic migraines.	[104]
4.	**Solid lipid nanoparticles**	Intravenous	Rapidly delivered drugs to the brain, decreased peripheral side effects, and offered considerable pain relief.	Speeds up the systemic circulation of drugs and lessens inflammation in the pathways that cause migraines.	treats intense migraine attacks that need to be treated right away.	[105]
5.	**Nanoemulsions**	Transdermal	Improved skin penetration and lower	Encourages the skin to absorb it for	With little side effects, it is	[106]

			systemic toxicity; regulated drug release.	localized or systemic therapeutic benefits.	appropriate for treating isolated migraines.	
6.	**Liposomes**	Nasal	Longer drug retention in the brain, lower systemic degradation, and better targeting of migraine-related areas.	Drugs are encapsulated in phospholipid bilayers for improved stability and precise brain delivery.	efficient at addressing the parts of the brain linked to pain in order to cure acute migraines.	[107]
7.	**Dendrimers**	Oral	Exhibited high drug loading and selective targeting; significantly reduced migraine-associated symptoms in vivo.	At migraine-related locations, a multibranched structure allows for precise medication delivery and regulated release.	prophylactic migraine treatment and long-term care.	[108]
8.	**Nanocrystals**	Intranasal	Improved solubility of poorly soluble medicines, resulting in a speedier onset of action and greater therapeutic efficiency.	Increases medication dissolving surface area, improving therapeutic activity and absorption**.**	Acute migraines should be treated quickly, especially if they start suddenly.	[109]

Future Prospective

Increasing Pathophysiology Knowledge: Further research into the physiological and molecular processes that underlie migraines is essential. Future studies should concentrate on microglial activation, neuroinflammatory processes, and the part cortical spreading depression (CSD) plays in the development of headaches and auras. One important field of research continues to be the interaction of epigenetic control and genetic variables in susceptibility and chronicity [110].

New Targets for Drugs: Creating therapies that target other pathways, like orexins, TRP channels, or PACAP, may offer choices with better safety and efficacy profiles. Further improvement of monoclonal antibodies and CGRP antagonists may further lessen side effects [111].

Personalized Medicine: Using biomarkers such as CGRP levels, genetic profiles, and imaging data to tailor treatments to individual patients could enhance efficacy while reducing adverse effects. Integrating polygenic risk scores and pharmacogenomics into clinical practice remains a priority [112].

Neuromodulation Developments: More widespread use and better results could result from research into improving non-invasive neuromodulation tools like vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS) [113].

Therapies in Combinations: Combining current medications, including triptans or gepants with CGRP monoclonal antibodies, may maximise efficacy while reducing the risk of tolerance or misuse [114].

Integration of Technology: Individualised treatment plans can be completely transformed by integrating digital health tools and artificial intelligence, such as wearables for migraine monitoring and prediction [115]

Research on Paediatric and Geriatric Migraines: There is an urgent need to prioritise age-specific therapeutic efficacy and safety in order to maximise results for both children and older adults [116].

CONCLUSION

Migraine is a complex neurological disorder involving neurovascular mechanisms, the trigeminovascular system, and CGRP. It progresses through premonitory, aura, headache, and postdrome phases. Peripheral and central sensitization contribute to pain amplification and prolonged symptoms. Genetic mutations and environmental triggers, such as stress and hormonal changes, influence susceptibility. Cortical spreading depression (CSD) plays a key role in aura migraines, disrupting the blood-brain barrier. Advances in neuroimaging and CGRP-targeted therapies have improved management, but further research is needed for personalized treatments. Migraine management has advanced with NSAIDs, triptans, and CGRP antagonists for acute relief, while beta-blockers, antidepressants, and CGRP monoclonal antibodies aid prevention. Non-pharmacological approaches, including lifestyle changes and neuromodulation, enhance treatment. Challenges remain, such as variable response and limited access to new therapies. Nanoformulations, including lipid nanoparticles, dendrimers, and polymeric nanoparticles, enhance the drug delivery and bioavailability, overcoming limitations of traditional treatments, while personalized medicine and AI-driven precision treatments are reshaping care. Future advancements will focus on new targets, neuromodulation, and tailored therapies, improving outcomes and quality of life.

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