Chapter

Recent Advances in Migraine Therapy

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Abstract

Migraine characterized by recurrent headache episodes presents with aura or without. Various treatment modalities ranging from 5-HT1B/1D agonists, non-steroidal anti-inflammatory drugs (NSAIDs), to steroids are available for acute treatment of migraine. Prophylaxis for chronic cases usually encompasses β blockers, calcium channel blockers, and antiepileptics. Many nutraceutical preparations are helpful in migraine, including riboflavin and vitamin B_{12}. This review focuses on the newer agents available for treatment of migraine with some insights into their clinical trials.

Keywords: headache, nutraceutical, prophylaxis, triptans, cortical spreading depression

1. Introduction

The word "migraine" comes from the Greek ἡμικρανία (*hemikrania*), "pain on one side of the head"; ἡμι- (*hemi-*), "half"; and κρανίον (*kranion*), "skull." The disorder may also be described as a vascular headache associated with changes in the size of the arteries within and outside the brain [1]. It is usually accompanied by a plethora of comorbidities influencing its clinical expression and complicating its treatment, making migraine a chronic and debilitating neurological disorder. It is a polygenetic disease with high susceptibility to epigenetic factors affecting millions of people worldwide. This is mainly because of changes in hormonal levels. It is estimated that up to 15% of people suffer from migraine worldwide with 1.4–2.2% affected by the chronic form of the disease [2, 3]. Global data shows the prevalence of migraine increasing during adolescence with peaks in midlife and the prevalence declining rapidly after 50 years. Migraine presents as headache and visual, auditory, olfactory, and cutaneous stimuli hypersensitivity along with nausea and vomiting [4]. Both environmental and genetic factors play a role in the development of migraine with more than two third of cases having familial history [5]. Boys are more affected than girls before puberty, but women are more affected than men as age increases [6].

2. Signs and symptoms

Migraine is self-limiting, usually presenting as recurrent severe headache. It is associated with autonomic symptoms. It presents with aura in 15–30% and without aura in the rest [7]. Migraine varies from person to person with respect to severity of pain, duration of attack, and its frequency. A migraine lasting longer than 72 h is

termed status migrainosus. Different phases of migraine include the prodrome, the aura, the pain, and the postdrome. The prodromal phase occurs hours before the headache in 60% of patients, the aura usually precedes headache in 15–20%, severe headache occurs in the pain phase, and the postdromal phase usually follows the attack of migraine [8].

3. The pathophysiology of migraine

The best solutions to medical conditions come only from understanding the pathophysiology of the disease state. As per Wolff's vascular theory, vascular constriction leading to hypoperfusion of the cortex later followed by vascular dilation was put forward as the main pathophysiological mechanism. Currently neurovascular hypothesis involving the trigeminovascular system is considered. Another hypothesis includes mutations of neuronal calcium channels, leading to hypersensitivity, resulting in migraine attacks. It is also postulated that increased dopaminergic activity in the thalamus/hypothalamus causing modulation in central pain pathways also plays a role in migraine attacks. Other mechanisms put forward include cortical spreading depression; release of vasoactive peptides like substance P, calcitonin gene-related peptide (CGRP) from trigeminal neural endings, nitric oxide, and serotonin; excess activation of N-methyl-D-aspartate receptor (NMDA) receptors without modulation by brain stem pain centers due to dysfunction of these centers; overactivity of excitatory neurotransmitters like aspartate and glutamate causing neuronal excitability; and finally neurogenic inflammation which play an important role in migraine attack development [9–12].

4. Treatment of migraine

It can be divided into treatment of acute attacks and treatment of chronic migraine. As per the US consortium (2000), recommended guidelines [13] for treatment of acute migraine include pharmacological and non-pharmacological modalities as shown in **Table 1**.

1. Specific treatment
a. Triptans
b. Ergot and its derivatives
2. Nonspecific treatment
a. Antiemetics
b. NSAIDs and nonnarcotic analgesics
c. Narcotics/opiate analgesics

Table 1.
Treatment of acute migraine attacks.

5. Specific treatment

5.1 Triptans

Triptans are selective agonists of 5-HT1B and 5-HT1D receptors. The mechanism of action includes intracranial vessel vasoconstriction (5-HT1B), peripheral neuronal inhibition (5-HT1D), and presynaptic dorsal horn stimulation (5-HT1D), producing second-order brain stem neuronal inhibition. Triptans influence the function

Drugs	Half life	Maximum daily dose
Group 1: fast-acting triptans		
Sumatriptan	3 h	200 mg oral 40 mg intranasal 12 mg subcutaneous
Rizatriptan	2–3 h	30 mg (15 mg if on propranolol)
Almotriptan	3–4 h	25 mg
Zolmitriptan	3 h	Two tablets or 10 mg maximum oral daily dose. Two sprays or 10 mg intranasal
Eletriptan	4 h	80 mg
Group 2: slow-acting triptans		
Frovatriptan	26 h	7.5 mg
Naratriptan	6 h	5 mg

Table 2.
Triptan characteristics.

of 5-hydroxytryptamine 1F (5-HT1F) receptors and enhance descending inhibitory pain pathways. Triptans reduce—to a considerable extent—pain severity in 2 h as per randomized controlled trials. Oral formulations are usually preferred over other formulations, but 6 mg subcutaneous injection of sumatriptan appears to be the most efficacious. As per current evidence, all oral formulations have equal efficacy except for frovatriptan which is less efficacious but has longer duration action. Parenteral preparations are more useful than oral ones, but the choice of medications depends on the clinician as well as the patient. Triptans are the first-line drugs used in acute treatment of moderate-to-severe migraine with the best pain relief occurring if it is taken within 30 min of attack, and a second dose is usually recommended after 2–4 h of initial dose. It is best used in combination with antiemetics and NSAIDs. Adverse effects include serotonin syndrome when used in combination with selective serotonin reuptake inhibitors (SSRIs), and it should be used with caution in patients having ischemic heart disease [14–22]. Characteristics of triptans are summarized in **Table 2**.

6. Ergot and derivatives

Ergots act on multiple receptors including the 5-HT ones, and these account for a robust side effect profile. It is used in acute management of migraine. Side effect includes nausea as well as severe vasoconstriction. It is contraindicated in patients with vascular disease, hepatic problems, renal dysfunction, and hypertension. It is avoided in pregnancy. Dihydroergotamine (DHE) is the only preparation available and is used both parentally and intranasally. Repeated administration of DHE is very effective in refractory cases as well as status migrainosus. It is relatively safe and effective but it requires hospital administration [23–25].

7. Nonspecific treatment

7.1 Nonsteroidal anti-inflammatory drugs

Good quality evidence supports the use of NSAIDs alone or in combination with specific agents. These drugs in combination with antiemetics are comparable to

Drugs	Formulation	Dose used (the dose wording should be mg')
Aspirin	Tablet/oral solution	650–1000 mg
Ketorolac	Tablet	10 mg
Ketoprofen	Capsule	50–75 mg
Ketoprofen-extended release	Capsule	200 mg
Diclofenac potassium	Tablet/powder	50 mg
Meclofenamate	Capsule	50 mg, 100 mg
Ibuprofen	Capsule, tablet, oral suspension	400–1, 0 g
Etodolac	Tablet/capsule	200–500 mg
Naproxen	Tablet	120–550 mg
Naproxen-controlled release	Tablet	750–850 mg maximum

Table 3.
NSAID characteristics.

lower doses of oral triptans. Recently, powdered preparation of diclofenac sodium is approved for treatment of acute attack. Ketorolac, administrated IV, can be used for emergency management of migraine. NSAIDs need to be used with caution in patients with renal toxicity [26–29]. Characteristics of different drugs in this group are summarized in **Table 3**.

7.2 Neuroleptics/antiemetics

Dopamine D2 receptor antagonists can be used alone or in combination to treat headache as well as nausea. It is mostly used in emergency settings and is available in oral, parenteral, and suppository forms, but concerns over extrapyramidal side effects, tardive dyskinesia, and lack of familiarity in their effect on migraine attacks restrict their use to a great extent [30–33]. Characteristics of antiemetics are summarized in **Table 4**.

7.3 Corticosteroids

Steroids are suggested for acute treatment as well as for status migrainosus [34]. They act by reducing the neurogenic inflammation and vasogenic edema and also play an important role in central serotonergic pathways [35]. One study showed that addition of dexamethasone 4 mg per oral to triptans plus NSAID reduces recurrence and is well tolerated in patients with frequent attacks [36, 37].

Drug	Formulation	Dose of migraine
Prochlorperazine	Tablet, suppository	5–10 mg 25 mg
Metoclopramide	Tablet	10 mg
Chlorpromazine	Tablet	10–25 mg
Promethazine	Tablet	25–50 mg
Ondansetron	Tablet, oral disintegrating tablet	4 mg 8 mg

Table 4.
Antiemetic characteristics.

7.4 Opioids

Opioids are the most prescribed drug for acute and rescue therapy in migraine in America. Recent studies have discouraged the use of opioids mainly because it decreases gray matter, increases CGRP release, releases pro-inflammatory peptides, and also causes glutamate receptor activation. It also results in degranulation of mast cells and causes vasodilation. There are many side effects, such as overuse headache and disease progression [38, 39].

8. Newer agents

8.1 CGRP antagonists

Based on migraine pathology theories, trigeminal ganglion activation causes the activation of nociceptive neurons which leads to subsequent release of CGRP. Increased CGRP levels cause plasma protein extrusion, vasodilation, and mast cell degranulation, ultimately leading to neurogenic inflammation. Drugs which antagonize CGRP include olcegepant, telcagepant, and latest approved monoclonal antibodies, namely, erenumab, fremanezumab, and galcanezumab [40]. They prevent binding of endogenous CGRP on its receptors and suppress the stimulation of CGRP on trigeminal ganglion neurons. They inhibit cortical spreading depression [40]. They lack vasoconstrictive effect. Olcegepant is as effective as oral triptans with less cardiovascular side effects such as blood pressure increase and tachycardia. But one major limitation is intravenous dosing. Telcagepant was initially claimed to be as potent as rizatriptan, causing pain relief in 2 h and also sustained pain relief at 24 h and relief of migraine-associated symptoms with overall good tolerability profile, but later the phase II trial was terminated, claiming the drug showed increase in liver transaminases [40]. Eptinezumab is a new drug in this class under trial and is not yet approved by the Food and Drug Administration (FDA).

8.2 Lasmiditan

It is a 5-HT1F receptor agonist. In experimental model, it blocks neurogenic inflammation, decreases c-fos expression, and lacks vasoconstriction. The main postulated mechanisms include inhibition of protein leakage, blockage of secondary trigeminal neuronal activation, and inhibition of neuropeptide release like glutamate. In a double-blind placebo-controlled parallel group study in 512 patients, the oral form and dose of 50, 100, 200, and 400 mg in moderate-to-severe migraine attacks proved that it is as effective as sumatriptan without causing vasoconstriction, but the significant drawback is its major side effects in the central nervous system. Studies also show a great improvement in headache response in 2 h but also show high 24-h headache recurrence rate [41].

8.3 Tezampanel

Tezampanel acts as a competitive antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptor (subtype $GluR_5$) of the ionotropic glutamate receptor family. A randomized triple-blind parallel group double-dummy, multicenter trial showed 1.2 mg tezampanel had 69% headache response rate when compared to 6 mg s.c. sumatriptan which had a response rate of 86%. It is effective and well tolerated in migraine. It can be used only via intravenous route. Dasolampanel is an orally bioavailable analog of tezampanel. Both drugs were never marketed [42]. Other newer agents are summarized in **Table 5**.

Newer targets and drugs	Current status
1. Adenosine receptor agonists [43]	• GR79236 and GR190178 • GR79236: carotid vasoconstriction than prejunctional inhibition of CGRP release
2. NXN-188 [44]	• A selective nNOS inhibitor + 5-HT1B/5-HT1D receptor agonist inhibits CGRP release in preclinical animal models
3. LY2951742 [45]	• Monoclonal antibody to CGRP under trial
4. Orexin receptor antagonism [46] (filorexant)	Orexin: trigeminal nociceptive and CSD RCT: failed efficacy
5. TRPV1 antagonism (SB-705498) [47]	• Trigeminal nociceptors: heat- and capsaicin-gated channel TRPV1 • Peripheral and central sensitization of trigeminovascular system
6. Melatonin [48]	• Abnormal levels: decreased inhibitory neurotransmission • Decrease inhibition of release of CGRP
7. P2Y purinergic receptors [49]	• Involved in pain signaling and future receptor target

Table 5.
Newer targets and drugs.

8.4 Prophylaxis

It is indicated when a patient meets the following criteria [50]:

- Four or more migraine days per month.
- Recurring migraines significantly interfere with daily activity.
- Contraindication/failure/overuse—acute therapies.
- Overwhelming costs of acute therapies.
- Uncommon migraine conditions—hemiplegic and basilar migraine.

8.5 Beta blockers

Various beta blockers used are summarized in **Table 6**. The mechanisms by which they act include inhibition of central beta receptors and antagonism of 5-HT1A and 5-HT1B receptors, thereby reducing neuronal excitability. It inhibits nitric oxide (NO) production by blocking inducible nitric oxide synthase and

Drugs	Daily doses
Propranolol	40–400 mg
Nadolol	20–160 mg
Metoprolol	100–200 mg
Atenolol	50–200 mg
Timolol	20–60 mg

Table 6.
Beta blockers and dosage.

Drugs	Comment
1. Flunarizine	• 5–10 mg (bedtime) • Used in Europe
2. Verapamil	• 120–640 mg (bid/tid) • 2 trials have shown efficacy better than placebo but more randomized trials to prove its efficacy [55]

Table 7.
Calcium channel blockers and dosage.

inhibits excitatory activity of glutamate, thereby reducing neuronal activity. They also inhibit kainate-induced currents (synergistic with NMDA blockers) and reduce neuronal activity and also have additional membrane-stabilizing action [51, 52].

8.6 Carvedilol: novel β blocker in migraine

In an open-label trial of 76 patients, a dose of 3.125–6.25 mg twice a week was used, and it was found that 60% of patients had 50% reduction in monthly migraine attack frequency and severity, but in 26% of patients, there was lack of efficacy with the drug [53].

8.7 Calcium channel blockers

It inhibits calcium entry and prevents intoxication of cells exposed to cerebral hypoxia due to cortical spreading depression [54]. Various drugs used are summarized in **Table 7**. Other possible mechanisms include inhibition of 5-HT release, inhibition of neurovascular inflammation, and cortical spreading depression.

9. Antiepileptics

9.1 Divalproex sodium

It is a combination of valproic acid and sodium valproate. It is used at a dose of 500–1500 mg/day. Mechanisms include prolongation of sodium channel inactivation, suppression of calcium-mediated T current, and inhibition of gamma-aminobutyric acid (GABA) transaminase. Adverse effect includes nausea, vomiting, gastrointestinal distress, alopecia, and craniofacial abnormalities in fetus [56].

9.2 Topiramate

Topiramate is a recently approved drug for migraine prophylaxis. Starting dose of 15–25 mg at bedtime and increase 15–25 mg/week [57]. Mechanisms include blocking of the voltage-gated sodium channel and inhibition of activation of AMPA-kainate receptor of glutamate, and it also enhances postsynaptic $GABA_A$ receptor current. Adverse effects include somnolence, fatigue, weight loss, nervousness, and precipitation of renal calculi.

9.3 Tiagabine

It inhibits GABA transporter (GAT-1) and thereby reduces GABA uptake into the neurons and glia. It is still not approved by the FDA. In an open-label trial of

41 patients who failed with treatment of valproates with 4 mg QID, 33/41 patients showed 50% reduction in migraine attacks, and 5 patients showed complete remission in migraine [58].

9.4 Levetiracetam (LCT)

It modifies synaptic release of glutamate/GABA by binding to specific synaptic protein (SV_2A). Anecdotal evidence says prevention of migraine. A 10-week open-label study, evaluating efficacy and safety of LCT for pediatric migraine in a population of 30 children or adolescents aged 6–19 years, showed a reduction in headache frequency and severity [59].

9.5 Zonisamide

It blocks voltage-dependent sodium and T-type calcium channels and decreases glutamate-mediated excitatory neurotransmission. Also, it inhibits excessive NO production and helps in scavenging NO and hydroxyl radicals. In an open-label trial, 33 patients with migraine headache, refractory to other preventive therapies, were given a dose of 100–600 mg every third day. Results showed that 65% of patients had a reduction in frequency of migraine attacks [60].

9.6 Antidepressants

Possible mechanisms include reuptake inhibition of serotonin and noradrenaline, α-adrenergic and NMDA-receptor antagonism, sodium and calcium channel blocking action, and potassium channel activation. Increase in $GABA_B$ receptor action and opioid receptor binding/opioid-mediated effect is another minor action. It reduces inflammation by decreasing prostaglandin (PGE_2) and tumor necrosis factor (TNF-α). Various drugs are summarized in **Table 8**. Venlafaxine is used at a dose of 75–225 mg: a double-blind placebo controlled trial showed that the drug was better than placebo, starting with 37.5 mg extended release tablet/week followed by 75 mg for another week and then 150 mg extended release in the morning [61].

9.7 Drugs acting on renin-angiotensin system

The renin-angiotensin system plays a role in neurogenic inflammation and causes increased susceptibility to oxidative stress. It also causes endothelial dysfunction and neuromodulator in nociception. Lisinopril alters sympathetic activity and inhibits free radical activation. It also increases prostacyclin synthesis and blocks the degradation of bradykinin, substance P, and encephalin. In a double-blind placebo-controlled crossover study, patients aged 19–59 years with migraine were treated with 20 mg Lisinopril for 11 weeks—21% of patients showed 50% reduction in migraine attacks [62]. In a comparative study of candesartan vs

Drugs	Daily doses
Amitriptyline	10–400 mg
Doxepin	10–300 mg
Nortriptyline	10–150 mg
Protriptyline	5–60 mg

Table 8.
Antidepressant dosage.

propranolol for migraine prophylaxis in 72 patients, 43% of patients showed greater than 50% reduction in migraine, and it was equally efficacious to propranolol [63].

9.8 Onabotulinum toxin

It is the FDA-approved drug for prophylaxis of chronic migraine at doses ranged from 155 to 195 IU, and it is injected in seven craniofacial and neck muscles, usually the temporalis. It inhibits neurogenic inflammation by inhibiting the release of nociceptive mediators like glutamate, substance P, and CGRP from the peripheral terminals of the efferent nerves. The analgesic action of onabotulinum toxin is central but yet to be proved. It will effect 3 h after injection and last for at least 7 days. Novel delivery routes such as topical/subcutaneous applications are under research [64].

9.9 H_3 agonists

It is used to limit the excessive inflammatory response through H_3 receptor activation. Drugs include Nα-methylhistamine and investigational drug SCH 50971. Phase III double-blind placebo-controlled trial for 12 weeks in 60 patients with a dose of 1–3 mg twice a week caused a reduction in headache frequency, intensity, and duration in 80% of patients. It helps in reducing the dose of analgesics used [65].

9.10 Tonabersat

Preclinical studies showed inhibition of cortical spreading depression by the drug. It inhibits neurogenic inflammation and also the gap junctional intercellular communication (GJIC) between the neurons and satellite glial cells. Various randomized double-blind parallel group placebo-controlled multicenter studies for acute migraine were tried. There are conflicting reports of headache relief at 2/4 h and reasons are not found. In one study with 40 mg on 39 patients, it was found to be effective for migraine with aura when compared to that without it, reinforcing its inhibitory effect on CSD [66].

10. Nutraceuticals in migraine

10.1 Magnesium

Multiple studies show migraine is associated with low levels of magnesium. It causes an influx of calcium into the neurons, causing glutamate release into the neurons, which results in neuronal activation. The onset and propagation of cortical spreading depression is delayed and decreases. It also causes change in neurotransmitter secretion and intensifies the secretion of substance P. It is used in patients with aura and premenstrual migraine and is used at a dose of 1, 0 g IV and 300–600 mg orally in chelated magnesium (taurate, glycinate, oxide) [67]. Magnesium plus L-carnitine is a newer preparation available.

10.2 Coenzyme Q10 (CoQ)

It promotes electron transfer from complex I and II to cytochrome C and helps in ATP production. It protects the mitochondria from free radical damage. A study of 1478 migraine patients of age range 3–22 years showed low levels of CoQ in 33%

of patients. A randomized controlled trial of 42 patients receiving 100 mg TID for 3 months found it superior to placebo, and 48% of subjects have greater than 50% reduction in migraine attacks [68].

10.3 Riboflavin

It is a cofactor in the Krebs cycle. Abnormal phosphorylation of ADP to ATP is prevented with riboflavin. A randomized controlled trial with 400 mg riboflavin taken daily for 3 months was superior to placebo for reduction of migraine frequency [69]. A randomized controlled trial with 400 mg of riboflavin plus feverfew and low-dose magnesium was comparable to a 25 mg active riboflavin. Greater than 40% of patients showed 50% reduction in migraine attacks [70].

10.4 Vitamin B_{12}

It helps in the conversion of homocysteine to methionine. Studies show vitamin B_{12} deficiency causes increase levels of urine methylmalonic acid levels in patients and worsens migraine. A possible mechanism of vitamin B_{12} action in migraine includes its excitatory role in the CNS by acting on NMDA receptors. It also plays a significant role in initiation, duration, and progression of migraine and activation of trigeminovascular system [71].

10.5 Feverfew

It is sold as capsules of dried leaves of the weed plant *Tanacetum parthenium*. Animal models show feverfew acts by inhibition of nitroglycerine-induced fos expression and inhibition of nuclear factor-kappa β. An open-label trial with *T. parthenium* (300 mg) plus *Salix alba* (white willow) for 12 weeks showed a decrease in pain intensity and duration of migraine. A randomized double-blind placebo-controlled trial (riboflavin 400 mg + magnesium 300 mg + feverfew 100 mg) for 3 months showed positive results. Recently two randomized clinical trials (RCT) of a purified stable extract of feverfew, MIG99, were ineffective in migraine, and clinical effects were very low with various complications [72].

10.6 Petasites (butterbur root)

Petasites hybridus is a potential poisonous plant but the detoxified root extract is safe. Mechanisms include inhibition of the synthesis of leukotrienes. It also decreases the intracellular concentration of calcium. It is used in the prophylaxis of migraine in children. A small study of 100 mg/day and a larger one of 150 mg/day vs placebo have shown efficacy [73].

11. Conclusion

With many newer agents now under clinical trials as well as in use, physicians should be aware of these drugs and their side effects, so they can use these agents for treating recurrent and chronic cases of migraine. Also, further well-designed clinical trials are needed to prove the efficacy of these agents in treatment of migraine. So, further research is needed to find out the safest and most effective treatment for chronic migraine, further designing proper animal models for studying migraine, to identify newer drug targets and how to prevent the migraine at the patient level from acute attack going in for chronic attack.

Conflict of interest

Nil.

Abbreviations

NSAIDS	nonsteroidal anti-inflammatory drugs
GJIC	gap junctional intercellular communication
CGRP	calcitonin gene-related peptide
NO	nitric oxide
NMDA	N-methyl-D-aspartate receptor
DHE	dihydroergotamine
ATP	adenosine triphosphate
ADP	adenosine diphosphate

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