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Review Article

A COMPLETE REVIEW OF MIGRAINE

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ABSTRACT

Migraine characterized by recurrent headaches present with aura or without aura. Various treatment modalities ranging from 5-hydroxytryptamine 1B/1D agonists, non-steroidal anti-inflammatory drugs to steroids are available for acute treatment of migraine. Prophylaxis for chronic cases is usually with β blockers, calcium channel blockers, and antiepileptics. Even many nutraceutical preparations are helpful in migraine including riboflavin, vitamin b12. This review focuses on the newer agents available for treatment of migraine with some sight into their clinical trials.

Keywords: Headache, Nutraceutical, Prophylaxis, Triptans, Cortical spreading depression.

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INTRODUCTION

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

SIGNS AND SYMPTOMS

Migraines are 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 hrs is termed status migrainosus. Different phases of migraine include the prodrome, aura, pain, and 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 postdromal phase usually follows the attack of migraine [8].

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 cortex later followed by vascular dilation was put forward as the main pathophysiological mechanism. Currently, neurovascular hypothesis involving the trigeminovascular system is considered. Other hypothesis includes mutations of neuronal calcium channels leading to hypersensitivity resulting in migraine attacks. It is also postulated that increased dopaminergic activity in thalamus/hypothalamus causing modulation in central pain pathways also plays a role in migraine attacks. Other mechanisms put forward include cortical spreading depression (CSD), release of vasoactive peptides like substance P, calcitonin gene-related peptide (CGRP), from trigeminal neurons, nitric oxide (NO), serotonin, excess activation of N-methyl-D-aspartate receptor (NMDA) receptors without modulation by brain stem pain centers due to dysfunction of these centers, over activity of excitatory neurotransmitters such as aspartate, and glutamate causing neuronal excitability, and finally, neurogenic inflammation plays an important role in migraine attack development [9-12].

TREATMENT OF MIGRAINE

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

Specific treatment

Triptans

Triptans are selective agonists at 5-hydroxytryptamine 1B (5-HT1B) and 1D. 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 of 5-HT1F receptors and enhance descending inhibitory pain pathways. Triptans reduce pain severity in 2 hrs as per randomized controlled trials (RCTs). Oral formulations are usually preferred over other formulations, but 6 mg subcutaneous injection of sumatriptan appears to be the most efficacious. As per the 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 then oral preparations, but the choice of medications depends on clinician as well as the patient. Triptans are the first-line drugs used in acute treatment of moderate–to-severe migraine with best pain relief occurring if it is taken within 30 minutes of attack, and a second dose is usually recommended after 2-4 hrs of initial dose. It is best used in combination with antiemetics and non-steroidal anti-inflammatory drugs (NSAID's). Adverse effects include serotonin syndrome when used in combination with selective serotonin reuptake inhibitors and it should be used with caution in patients having ischemic heart disease [14-22]. Characteristics of triptans are summarized in Table 2.

Ergot and derivatives

Ergots act on multiple receptors including 5HT, and this accounts for robust side effect profile. It is used in acute management of migraine. Side effect includes nausea as well as due to severe vasoconstriction. It

is contraindicated in patients with vascular disease, hepatic problems. renal dysfunction, and in hypertensives. It is avoided in pregnancy. Dihydroergotamine (DHE) is the only preparation available and is used both parentally as well as intranasally. Repeated administration of DHE is very effective in refractory cases as well as status migraine. It is very safe and effective, but it requires hospital administration [23-25].

Non-specific treatment

NSAIDs

Good quality evidence supports the use of NSAID's alone or in combination with specific agents. NSAID's in combination with antiemetics are comparable to oral triptans. Recently, powdered preparation of diclofenac sodium is approved for treatment of acute attack. Intravenous (IV) ketorolac can be used for emergency management of migraine. NSAID's needs to us be used with caution in patients with renal toxicity [26-29]. Characterized of different NSAID's are summarized in Table 3.

Neuroleptics/antiemetics

Dopamine d2 receptors antagonists can be used alone or in combination to treat headache as well as to treat 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 restricts their use to a great extent [30-33]. Characteristics of antiemetics are summarized in Table 4.

Corticosteroids

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

Opioids

It is 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. Side effects are also high and result in overuse headache and disease progression [38,39].

NEWER AGENTS

CGRP antagonists

Based on migraine pathology theories, trigeminal ganglion activation causes 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, MK-3207, and BI-44370TA [40]. Prevents binding of endogenous CGRP on its receptors and suppresses the stimulation of CGRP on trigeminal ganglion neurons. It inhibits CSD. They lack vasoconstrictive effect. Olcegepant is as effective as oral triptans with less cardiovascular side effects such as blood pressure increase and tachycardia. However, one major limitation is IV dosing. Telcagepant was initially claimed to be as potent as rizatriptan causing pain relief in 2 hrs and also sustained pain relief at 24 hrs and relief of migraine-associated symptoms with overall good tolerability profile, but later, the Phase 2 trial was terminated claiming the drug showed increase in liver transaminases [40].

Lasmiditan

It is a 5-HT1F receptor agonist. In experiment model, it blocks neurogenic inflammation, decreases c-Fos expression, and lacks vasoconstriction.

Table 1: Treatment of acute migraine attacks

Specific treatment
Triptans
Ergot and its derivatives
Non-specific treatment
Antiemetics
NSAIDs and non-narcotic analgesics
Narcotics – Opiate analgesics

NSAID: Non-steroidal anti-inflammatory drugs

Table 2: Triptan characteristics

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

Table 3: NSAID's characteristics

Drugs	Formulation	Dose used
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 mg
Etodolac	Tablet/capsule	200-500 mg
Naproxen	Tablet	120-550 mg
Naproxen-controlled release	Tablet	750-850 mg maximum

NSAID: Non-steroidal anti-inflammatory drugs

Table 4: Antiemetics characteristics

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

Main postulated mechanisms include inhibition of protein leakage, blockage of secondary trigeminal neuronal activation, and inhibition of neuropeptidase release like glutamate. Double-blind placebo controlled parallel group study in 512 patients: Oral form and dose of 50, 100, 200, and 400 mg in moderate–to-severe migraine proved that is as effective as sumatriptan without causing vasoconstriction, but major drawback is major central nervous system (CNS) side effects. Studies also show

Table 5: Newer target and drugs

Newer targets and drugs	Current status
Adenosine receptor agonists [67]	GR79236 and GR190178 GR79236: Carotid vasoconstriction than pre-junctional inhibition of CGRP release
NXN-188 [68]	A selective nNOS inhibitor+5-HT1B/1D receptor agonist, inhibits CGRP release in preclinical animal models
LY2951742 [69]	Monoclonal antibody to CGRP – under trial
Orexin receptor antagonism[70] (filorexant)	OREXIN: Trigeminal nociceptive and CSD RCT: Failed efficacy
TRPV1 antagonism (SB-705498) [71]	Trigeminal nociceptors – heat and capsaicin-gated channel TRPV1 Peripheral and central sensitization of trigeminovascular system
Melatonin [72]	Abnormal levels: decreased inhibitory neurotransmission Decrease inhibition of release of CGRP
P2Y purinergic receptors [73]	Involved in pain signaling and future receptor target

CGRP: Calcitonin gene-related peptide, RCT: Randomized controlled trials

high improvement in headache response in 2 hrs but also show high 24-h headache recurrence rate [41].

Tezampanel

- 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. Randomized triple-blind parallel group double dummy, multicenter trial showed that 1.2 mg/kg tezampanel had (69%) headache response rate when compared to 6 mg/kg s.c sumatriptan which had a response rate of 86%. Effective and well tolerated in migraine. It can be used only through IV route dasolampanel is an orally bioavailable analog of tezampanel. Both the drugs were never marketed [42].
- Other newer agents are summarized in Table 5.

Prophylaxis

It is indicated when a patient meets the following criteria [43]:

- 2 or more attacks/month
- Recurring migraines – significantly interfere with daily activity
- Contraindication/failure/overuse-acute therapies
- Overwhelming costs of acute therapies
- Uncommon migraine conditions – hemiplegic, basilar migraine.

Beta-blockers

Various beta-blockers used are summarized in Table 6. The mechanisms by which they act include inhibition of central beta receptors antagonize 5-HT1A and 5-HT1B receptors thereby reducing neuronal excitability. Inhibits NO production by blocking inducible NO synthase and 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 [44,45].

Carvedilol - Novel B-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 was found that 60% of patients had 50% reduction in monthly migraine attack frequency and severity, but in 26% patients, there was a lack of efficacy with the drug [46].

Calcium channel blockers

Inhibits calcium entry and prevents intoxication of cells exposed to cerebral hypoxia due to CSD [47]. Various drugs used are summarized in Table 7. Other possible mechanisms include inhibition of 5-HT release, inhibition of neurovascular inflammation, and CSD.

ANTIEPILEPTICS

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, inhibit gamma-aminobutyric acid (GABA) transaminase.

Table 6: Beta blockers and dosage

Drugs	Doses
Propranolol	40-400 mg
Nadolol	20-160 mg
Metoprolol	100-200 mg
Atenolol	50-200 mg
Timolol	20-60 mg

Table 7: Calcium channel blockers and dosage

Drugs	Comment
Flunarizine	5-10 mg (bed time) Used in Europe
Verapamil	120-640 mg (BID/TID) 2 trials have shown efficacy better than placebo but more randomized trials to prove its efficacy [48]

Adverse effect includes nausea, vomiting, gastrointestinal distress, and alopecia [49].

Topiramate

It is the recently approved drug for migraine prophylaxis. Starting dose of 15-25 mg at bedtime and increase 15-25 mg/week [50]. Mechanisms include blocking of the voltage-gated sodium channel blockade 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 precipitate renal calculi.

Tiagabine

It inhibits GABA transporter 1 and thereby reduces GABA uptake into neurons and glia. Still not approved by the Food and Drug Administration (FDA). In an open-label trial of 41 patients who failed with the treatment of divalproex with 4 mg QID, 33/41 patients showed 50% reduction in migraine attacks and 5 patients showed complete remission in migraine [51].

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 reduction in headache frequency and severity [52].

Zonisamide

It blocks voltage-dependent sodium and T-type calcium channels and decrease glutamate-mediated excitatory neurotransmission. Furthermore, inhibits excessive NO production and helps in scavenging NO and hydroxyl radicals. Open-label trial of 33 patients with migraine

headache and refractory to other preventive therapies were given a dose of 100-600 mg every 3rd day. Results showed 65% of patients reduction in frequency of migraine attacks [53].

Antidepressants

Possible mechanisms include reuptake inhibition of serotonin and nor adrenaline, 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 are other minor actions. Reduces inflammation by decreasing the synthesis of prostaglandin E2 and decreasing the level of tumor necrosis factor 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 venlafaxine better than placebo. Start with 37.5 mg extended release tablet/week followed by 75 mg for another week, then 150 mg extended release in the morning [54].

DRUGS ACTING ON RENIN ANGIOTENSIN SYSTEM

Renin angiotensin system plays a role in neurogenic inflammation and causes increased susceptibility to oxidative stress. It also causes endothelial dysfunction and neuromodulation 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 [55]. In a comparative study of candesartan versus propranolol for migraine prophylaxis, 72-43% patients showed >50% reduction in migraine and it was equally efficacious to propranolol [56].

Onabotulinum toxin

FDA approved drug for prophylaxis of migraine at a dose of 100 IU. It is used in a chronic headache.

Moreover, it is injected in craniofacial muscles usually the temporalis. It inhibits neurogenic inflammation by inhibiting the release of nociceptive mediators such as glutamate, substance P, and CGRP from peripheral terminals of efferent nerves. The analgesic action of on a botulinum toxin is central yet to be proved. It is It is effective after three hours of injection and the action lasts for seven days. Novel delivery routes such as topical/subcutaneous applications are under research [57].

H_3 agonists

Used to limit the excessive inflammatory response through H_3 receptor activation. Drugs include Nα-methyl histamine and investigational drug SCH 50971. Phase III double-blind placebo controlled trial for 12 weeks in 60 patients with dose of 1-3 mg twice a week caused reduction in headache frequency, intensity, and duration in 80% of patients. Decreases in the use of analgesics was also noted [58].

Tonabersat

Preclinical studies show inhibition of CSD. It inhibits neurogenic inflammation and also inhibits the gap junctional intercellular communication between neurons and satellite glial cells. Various randomized double-blind parallel group placebo controlled multicenter studies for acute migraine were tried. Conflicting reports of headache relief at 2/4 hrs and reasons unfound. In one study with 40 mg on 39 patients, it was found to be effective for migraine with aura when compared to without aura, reinforcing its inhibitory effect on CSD [59].

Table 8: Antidepressants dosage

Drugs	Doses
Amitriptyline	10-400 mg
Doxepin	10-300 mg
Nortriptyline	10-150 mg
Protriptyline	5-60 mg

NUTRACEUTICALS IN MIGRAINE

Magnesium

Multiple studies show migraine is associated with low levels of magnesium. Magnesium causes influx of calcium into neurons causing glutamate release into neurons causing neuronal activation.

Onset and propagation of CSD are delayed and decreases. It also causes change in neurotransmitter secretion and intensifies the secretion of substance P. Used in patients with aura and perimenstrual migraine. Used at a dose of 1 g IV and 300-600 mg orally of chelated magnesium (taurate, glycinate, and oxide). Magnesium + L-carnitine are a newer preparation available [60].

Coenzyme Q 10 (CoQ)

It promotes electron transfer from Complex I and Complex II to cytochrome C and helps in adenosine triphosphate (ATP) production. Protects mitochondria from free radical damage. Study of 1478 migraine patients from 3 to 22 years of age showed low levels of CoQ in 33% of patients. Randomized control trial of 42 patients receiving 100 mg TID for 3 months found it superior to placebo and 48% of patients has >50% reduction in migraine attacks [61].

Riboflavin

It is a cofactor in the Krebs cycle. Abnormal phosphorylation of adenosine diphosphate to ATP is prevented with riboflavin. Randomized control trial with 400 mg riboflavin taken daily for 3 months was superior to placebo for reduction of migraine frequency [62]. Randomized control trial with 400 mg of riboflavin + feverfew+ low dose magnesium was comparable to a 25 mg of active riboflavin. Greater than 40% of patients showed 50% reduction in migraine attacks [63].

Vitamin B12

It helps in conversion of homocysteine to methionine. Studies show vitamin B12 deficiency that causes increase levels of urine methylmalonic acid levels in patients and worsens migraine. Possible mechanism of vitamin B12 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 [64].

Feverfew

It 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. Open-label trial with *T. parthenium* (300 mg) + *Salix alba* (white willow) for 12 weeks showed decrease in pain intensity and duration of migraine randomized double-blind placebo controlled trial (riboflavin 400 mg + magnesium 300 mg + feverfew 100 mg) for 3 months, positive results were seen. Recently two trials with purified stable extract of feverfew and MIG99 showed very low clinical effects with various complications and was ineffective in the treatment of migraine [65].

Petasites (butterbur root)

Petasites hybridus is a very poisonous plant, and detoxified root extract is safe. Mechanisms include inhibition of the synthesis of leukotrienes. It also decreases the intracellular concentration of calcium and used in the prophylaxis of migraine in children. A small study of 100 mg/day and larger study of 150 mg/day versus placebo have shown efficacy [66].

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. Furthermore, further well-designed clinical trials are needed to prove the efficacy of these agents in treatment of migraine. Hence, further research is needed to find out the safest and effective treatment for a chronic migraine, further designing of 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.

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