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Advances in Migraine

ABSTRACT

The history of migraine is probably as old as the human history but much remains to be known about it. It is ubiquitous, affecting people worldwide and significantly impacting their quality of life. Although the pathogenesis is still incompletely understood, it is considered to involve the trigeminovascular system and the pathophysiology is now described separately for different phases of migraine. Migraine is no longer considered a vascular disorder but a disorder of central nervous system processing. Further progress in the pathogenesis has been made after the discovery of various signaling molecules involved in the genesis of migraine attack. The field of migraine therapeutics has seen a lot of progress as well. Many new treatment modalities such as ditans, gepants, monoclonal antibodies against calcitonin gene-related peptide (CGRP) receptor or ligands have revolutionized the treatment of episodic migraine. Whereas Onabotulinum-A has emerged as a standard of care for chronic migraine, recent data on monoclonal antibodies against CGRP receptor or ligand are encouraging. In addition, neuro-modulatory devices and greater occipital nerve blocks have emerged as alternative treatment options for acute as well as preventive treatment of high frequency episodic, chronic, and refractory migraine. The present article aims to provide a comprehensive review of the advances in migraine and at the end describes how the current corona virus disease-19 pandemic has impacted the management of migraine.

Key words: Migraine, Treatment, Acute, Preventive, Pathophysiology

INTRODUCTION

The word "migraine" comes from the Greek word "hemicrania," meaning "half head" and corresponds to the unilateral headache seen in migraine.[1] The concept of migraine was originally based on a disturbance of the "four humours" of ancient Greek medicine.[1] In ancient Indian literature, the term that best defines migraine appears to be Ardhavbhedaka.[2] In Ayurveda classics, Ardhavbhedaka is mentioned under the heading of Shirorogas (painful conditions of the forehead). The word Ardhavabhedaka has three components viz. Ardha (half) + Ava (bad prognosis) + Bhedaka (breaking pain).[2] As per Chakrapani, Ardhavabhedak means "Ardha Mastaka Vedana or half head pain.[2] Sushruta defines Ardhavabhedak as severe pricking, piercing type of pain in one half of the head which is associated with giddiness and appears after a fortnight, 10 days or can appear suddenly any time.[3] Despite being such an ancient disease, much is still unknown about migraine. In the present review, we shall discuss the current understanding of migraine and its management including the advancements made during the past decade.

EPIDEMIOLOGY

Migraine is ubiquitous and estimated to affect approximately 1 billion people worldwide.[4] According to the Global Burden of Disease Study 2016, migraine happens to be the second leading cause of disability, accounting for more disability than all other neurologic disorders combined.[5] Worldwide, the 1-year period prevalence of migraine is around 15%.[4] Although the exact nationwide prevalence of migraine in India is unknown, studies from different parts of India have yielded different results. Two surveys in the South[6] and North[7] India have found 1-year prevalence around 25%. Another survey from East India however found the prevalence around 14%.[8] In contrast, a study from Kashmir Valley among the school children has found the prevalence of 27%.[9] Therefore, it seems that Indians have a higher prevalence of migraine.[6,7,9] Migraine and tension-type headache were the most prevalent neurological disorders in India, affecting about 488 million people in 2019.[10] Furthermore, the prevalence of migraine was higher in females aged 35–59 years than in males of the same age which peaked with age at around 40–44 years.[10] Despite the lack of definite data, there is evidence of a huge gap between diagnosis and treatment of migraine in India and the economic burden of migraine in our country is believed to be substantial.[7,10]

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DIAGNOSIS

Migraine is a clinical diagnosis and no investigation can prove or disprove it. The most widely used diagnostic criteria is the one suggested by the International classification of headache disorders 3rd edition (ICHD-3),[11] which provides criteria for the three main types of migraine; migraine without aura, migraine with aura, and chronic migraine (Table 1). The common clinical characteristics of migraine include a long duration of headache attack, lasting 4–72 h, unilateral location, and pulsatile quality with moderate to severe pain intensity and aggravation due to routine physical activity. Systemic symptoms such as photo and phonophobia are often present. About a quarter of migraine patients also complain of transient neurological symptoms in the form of aura that usually precedes or occurs concurrently with the headache which can be visual, sensory, language or motor, or comprise brainstem symptoms. Migraine patients with recurrent frequent headaches (and often with acute medication overuse) may transform into a chronic state consisting of headache for at least 15 days in a month (with at least 8 days of migraine). This has been categorized as chronic migraine. ICHD-3 allows concurrent diagnosis of chronic migraine and medication overuse headache. It is important that all mimickers of migraine should be ruled out by careful history and examination and if required by appropriate investigations.

Table 1 Diagnostic criteria for migraine

Migraine without aura (Earlier called common migraine , hemicrania simplex) At least five attacks fulfilling criteria B-D
A. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
B. Headache has at least two of the following four characteristics
1. Unilateral location.
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity
C. During headache at least one of the following
1. Nausea and/or vomiting
2. Photophobia and phonophobia
D.Not better accounted for by another ICHD-3 diagnosis
Migraine with aura (Earlier called classical migraine, ophthalmic, hemiparesthetic, hemiplegic or aphasic migraine) At least two attacks fulfilling criteria B and C
A. One or more of the following fully reversible aura symptoms
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal
B.At least two of the following four characteristics
1.At least one aura symptom spreads gradually over ≥ 5 minutes and /or two or more symptoms occur in succession
2.Each individual aura symptom lasts 5-60 minutes
3.At least one aura symptom is unilateral
4.The aura is accompanied or followed within 60 minutes by headache
C. Not better accounted for by another ICHD-3 diagnosis , and transient ischemic attack has been excluded.
Chronic migraine
A. Headache (tension type and /or migraine like) on ≥ 15 days per month for > 3months and fulfilling criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for migraine without aura and /or criteria B and C for migraine with aura
C. On ≥ 8 days per month for > 3 months fulfilling any of the following
1. Criteria for migraine without aura
2. Criteria for migraine with aura
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted by another ICHD-3 diagnosis

As per ICHD -3: reference 11

PATHOPHYSIOLOGY

The basic research in migraine has for long overwhelmingly focussed on vasculature, neurovasculature, and neurotransmission.[12] The exact pathophysiology still remains unknown but the current evidence definitely points to the fact that migraine is a central nervous system disorder and not a vascular disorder.[13] A practical way to understand the pathophysiology of migraine is to divide it into five phases and study the mechanism of each phase separately.[14,15] The five phases namely premonitory or prodromal, aura, headache, postdrome and interictal are not always mutually exclusive.[16]

Premonitory phase

The premonitory phase of migraine is defined as symptoms preceding 48 h of the headache.[17] Close to 80% of migraineurs have various premonitory symptoms which are infrequently reported unless asked as patients do not consider them to be a part of the disease process.[18] A wide array of symptoms including yawing, food craving, polyuria, cognitive changes, mood disturbances, and light sensitivity are experienced by the patients during the prodrome phase.[18-23] A functional magnetic resonance imaging (MRI) study found that the hypothalamus is significantly more active and shows increased coupling with various brain regions in the 24 h preceding the headache.[23] The role of the hypothalamus is further strengthened by the fact that its altered connectivity with other brain regions especially the brainstem might explain some of the prodromal symptoms such as changes in appetite, yawning, food craving, and polyuria.[23,24] The evidence for the involvement of other brain regions implicated in the premonitory phase of migraine comes from a PET study done during the early premonitory phase of nitro-glycerine induced migraine attacks.[24] It found activation of the midbrain tegmental area, substantia nigra, periaqueductal grey, dorsal pons, and several cortical areas, including the occipital, temporal, and prefrontal cortex.[24] The locus ceruleus[25] (sleep alterations, pain modulation, trigeminal nociceptive processing), visual cortex[26] (enhanced photosensitivity), rostral dorsal medulla[27] and periaqueductal grey[27] (nausea and vomiting), trigeminocervical complex[28]

and brainstem[29] (neck pain and stiffness) are also implicated in the pathophysiology of the premonitory phase.

Aura phase

Various population studies have found the prevalence of aura in migraine patients to be between 20–40%.[30] The aura may not occur in all headache attacks and sometimes can occur without the headache.[31] Although auras has been studied for much longer than the migraine headaches, the role of aura and its underlying pathophysiological mechanism for the rest of migraine headache continues to be controversial.[32] As early as in 1870, Dr. Hubert Airy studied his own visual auras and documented how they changed over time.[33] Aristides Leao in 1940s described the phenomenon of cortical spreading depression, known today as the cortical spreading depolarization (CSD) and widely believed to be the basic pathophysiological mechanism underlying the aura.[34] CSD is a bioelectrical phenomenon that can be triggered in animal models by electrical stimulation.[35] The trigger causes a depolarisation shift of ions including sodium, potassium, chloride, and magnesium and a release of neurotransmitters chiefly glutamate and dopamine.[30,35] This ion shift and neurotransmitter release cause neuronal dysfunction resulting in a regional increase in blood flow (hyperemia) followed by a relative lack of blood flow (oligemia).[31] A study using high-field functional MRI with continuous recording observed blood oxygenation level-dependent signal changes in patients during the visual aura. It concluded that an electrophysiological event such as CSD generates the aura in the human visual cortex.[36] A recent study suggested that the mechanisms underlying the visual aura appear to propagate in a linear fashion along the gyri or sulci rather than in a concentric fashion as usually depicted based on the studies done in animals.[37] CSD has been shown to occur in the human brain as a result of traumatic brain injury as well as stroke but so far the cooccurrence of CSD and aura has not been seen in the human brain.[30,38] Also, the role of CSD triggering the rest of the migraine or directly causing headache is still not fully clear.[30,38,39]

Headache phase

The predominant vascular theory implicating dilation of vessels being responsible for the throbbing pain of migraine has largely been debunked and studies in humans have not found any correlation between the heart rate or arterial pulsation with the throbbing pain.[40] The findings from many other studies also suggest a neuronal instead of vascular "pacemaker" of the throbbing pain in migraine.[41-44] Though many aspects of the pain processing system and the exact events leading to headache are still unknown; the trigeminovascular system is now believed to be the main mediator of the migraine pain.[31] The trigeminal afferents together with cervical afferents from the upper cervical dorsal root ganglion synapse on second-order neurons in the dorsal horn of the trigeminal nucleus caudalis and its cervical extension.[45] From there the second-order neurons project to the thalamus and other key regions of the central nervous system that modulates sensory processing before thalamocortical neurons relay sensory information to multiple cortical areas.[31,45] The hypothalamus is not only implicated in the premonitory phase but also in the headache phase.[46] There are specific cells within the hypothalamus that have been shown to inhibit pain signals coming from the trigeminocervical complex.[47] In one study a patient with migraine was followed for an entire month with daily functional imaging and it was found that hypothalamic activity increased in response to trigeminal nociceptive input in the 24 h leading up to an attack.[47] Furthermore, there was evidence of increased functional connectivity between the hypothalamus and spinal trigeminal nuclei during the premonitory and the pain phases.[46,47]

Postdrome phase

Also described sometimes as "the migraine hangover" the postdrome phase is a common but relatively understudied phase. Close to 80% of patients report non-headache symptoms such as fatigue, nausea, neck stiffness, difficulty concentrating, and light sensitivity during the 24–48 h following the resolution of headache.[31,48] It is suggested that the whole brain but especially the frontal lobes and hypothalamus is involved in the postdrome.[48] Studies have found cerebral hypoperfusion during migraine episodes including the postdrome phase, which may be contributing to the symptoms.[31,48] This hypoperfusion has been ascribed to the activation of the brainstem nuclei, resulting in widespread vasoconstriction.[48] An alternative explanation for this reduction in regional cerebral blood flow could be the persistent hypoperfusion that follows the bioelectric phenomenon of CSD.[49] It is worth noting that acute treatment and comorbidities do not appear to have any effect on the occurrence of the postdrome.[48]

Interictal phase

Many migraine patients are never completely symptom free. Symptoms such as photophobia, phonophobia, osmophobia, cognitive dysfunction, and dizziness in the interictal period can be troublesome.[32] Although the exact underlying neural mechanisms of these symptoms remain poorly understood, more than 20 networks have been identified as having altered resting stage functional connectivity.[50] These include various cortical areas,[50] the thalamus,[51] hypothalamus,[52] brainstem,[53] amygdala[54,55] and the cerebellum.[56] Thus it is now widely believed that there is a global alteration in the brain function not only in the headache phase but also in the apparently asymptomatic phases.[32]

MOLECULAR BASIS OF MIGRAINE

At a molecular level multiple neurotransmitters, neuropeptides, and neurochemicals play a role in the pathogenesis of migraine. The role of calcitonin gene-related peptide (CGRP) in spontaneous as well as triggered migraine attacks is well

known.[57] Blood levels of CGRP are elevated during attacks, and blocking the action of CGRP aborts the attack.[58] However, there is some evidence to suggest that CGRP has antioxidant and anti-inflammatory properties and thus the release of CGRP might be the part of an adaptive response to the oxidative stress and not necessarily pathogenic.[59] Overall the current view is that CGRP plays a key role in the pathophysiology of migraine through arterial vasodilation, neurogenic inflammation, and activation of meningeal nociceptors.[60] Pituitary adenylate cyclase-activating peptide (PACAP) can induce migraine-like headache when administered to patients also has a role to play.[50,61] It is present in the trigemino parasympathetic circuit, where it contributes to headache and associated autonomic symptoms.[61] It also has a role in the hypothalamus, where it modulates circadian rhythms and food anticipatory behavior.[62] Serotonin has been established as one of the most important mediators in the migraine pathophysiology for long and the triptans, (5-HT1B/1D receptor agonists) have stayed as the cornerstone of acute migraine treatment for decades now.[63] A few migraine symptoms notably yawning, nausea, and difficulty concentrating are believed to be mediated through dopamine.[32] The orexigenic system has been implicated in fatigue and the sleep disturbance in migraine.[64] Multiple neuroendocrine mediators, such as insulin, glucagon, leptin, and neuropeptide Y, have effects on the trigeminovascular system, linking changes in appetite, food cravings, and migraine.[32] Other emergent neurochemical systems that may be implicated in migraine include somatostatin, cholecystokinin, antidiuretic hormone, and melatonin.[17,32]

MANAGEMENT OF MIGRAINE

Pharmacologic therapy stays as the cornerstone of migraine management and includes acute and preventive medications. Nonpharmacologic therapies such as resting in a quiet, dark room, hydration, special oils and biofeedback are mainly used as adjuncts to medication but in special situations like in pregnancy can be used as stand-alone preventive treatment.[65,66] As a general rule, medications used to alleviate the migraine pain are to be administered early on in the attack i.e., when the headache is still mild.[66] As regards the efficacy, the 2 h pain-free response and sustained pain-free response (i.e., freedom from pain with no recurrence or use of rescue medication 2–24 h post dose) provide the most clinically relevant information about the efficacy of acute migraine pharmacotherapy.[67] Furthermore, knowing and addressing the most bothersome migraine symptom (MBS) helps in better management of patients. In fact, the MBS has emerged as an important coprimary efficacy endpoint in clinical trials of acute treatments for migraine.[68]

Migraine attacks tend to recur and long-term management often requires preventive treatment. The goal is not to "cure" the migraine but reduce the frequency, duration, and severity of migraine attacks.[65,66] Before a treatment is started, the clinician and the patient both should be clear about the treatment goals. Although there is not a fixed rule, a patient having two or more disabling or four or more non-disabling migraine attacks per month should be considered for preventive treatment.[65,66]

TREATMENT OF ACUTE ATTACKS

Many people self-manage mild migraine attacks with the help of over-the-counter drugs or other non-pharmacological means.[65] However, a moderate-to-severe attack often necessitates medical help.[69] If an attack is not treated in time it can be quite disabling and lead to increasing emergency room visits,[65] and most importantly increase the risk of migraine chronification.[70] The pharmacologic approach to migraine is directed mainly by the severity of the attacks, patient's comorbid conditions, drug preferences, the presence of associated nausea and vomiting, and the treatment setting (home or hospital).[65,66] For people with mild to moderate migraine attacks, a variety of treatment options are available as detailed below and summarized in Tables 2 and 3.

Acetaminophen

Most of the patients even before they consult a doctor have tried acetaminophen. For mild headaches, it has proven efficacy over placebo but one should be cautious of the side effects especially at higher doses.[71]

Nonsteroidal anti-inflammatory drugs

Aspirin, diclofenac, ibuprofen, naproxen, and other NSAIDS have been shown to be very effective in moderate to severe migraine headache attacks.[72] However, they have adverse effects more severe than those of paracetamol, especially gastrointestinal and renal.[72] Moreover, if used for more than 15 days a month there's a risk for medication overuse headache.[73]

Opioids

Opioids and butalbital-containing products have limited if any use in migraine, and most guidelines do not recommend them.[74]

Triptans

Triptans (selective 5-hydroxytryptamine, serotonin (5-HT) 1B/D agonists) are migraine-specific and recommended as the first choice drugs for moderate-to-severe migraine attacks across all guidelines.[65,72] Besides vasoconstriction, they cause serotonin agonism and reduction of trigeminal nerve activation. A meta-analysis of triptans for the acute treatment of migraine found that standard-dose triptans provide 2-h pain relief for 42–76% of patients, which are better outcomes than ergots, equal to or better than NSAIDs and equal to or worse than combination medications.[75,76] However triptans have lesser tolerability when compared to non-triptans, have significant drug interactions, and are contraindicated in patients with a history ischemic heart disease, strokes, cardiac accessory conduction pathway arrhythmias, coronary artery vasospasm, uncontrolled hypertension, severe hepatic impairment, and

Table 2 Drugs for acute migraine attack

Drug and dosage	IAN[79]	AHS[80]	EHF[81]	CHS[82]
Acetaminophen (1000mg)	Not mentioned as first line	Strongly recommended	Recommended only as an alternative to NSAIDS	Strongly recommended
Aspirin (300-500mg)	Recommended (dosage not mentioned)	Strongly recommended	Strongly recommended (Dose 900-1000mg)	Strongly recommended
Ibuprofen (200-400 mg)	Recommended	Strongly recommended	Strongly recommended (Dose 400-800)	Strongly recommended
Diclofenac (50-100mg)	Recommended	Strongly recommended	Strongly recommended	Strongly recommended
Naproxen (500 or 550 mg)	Recommended	Strongly recommended	Recommended only in combination with Sumatriptan	Strongly recommended
Triptans	Strongly recommended	Strongly recommended	Strongly recommended	Strongly recommended
Ergotamine (1mg)	Recommended	Not mentioned	Not recommended	Not mentioned
Dihydroergotamine (Injection)	Recommended	Recommended as an agent with medium efficacy	Not recommended	Recommended as an agent with weak efficacy
Codeine	Only as rescue	Recommended as agent with medium to weak efficacy	Recommended against	Recommended against
Tramadol	Only as rescue	Recommended as an agent with medium efficacy	Recommended against	Recommended against

IAN: Indian Academy of Neurology; AHS: American headache society; EHF: European headache federation CHS: Canadian headache society

Table 3 Commonly used Triptans

Triptan	Usual oral dose /maximum daily dose
Sumatriptan	25mg, 50mg , 100mg / 200mg
Rizatriptan	5mg, 10mg / 30mg
Zolmitriptan	2.5mg, 5 mg/10 mg
Naratriptan	1mg,2.5mg/ 5mg
Almotriptan	6.25mg,12.5 mg/ 25mg
Eletriptan	20mg, 40mg/ 80 mg

Adapted from reference 76

ischemic bowel disease.[77] They also carry a risk of medication overuse headache if used for more than 10 days a month.[73]

Ergots

Ergots are among the oldest drugs for migraine but are prescribed rarely nowadays because of their poor tolerability, potential adverse effects, and the availability of better alternatives.[72] Dihydroergotamine (5-HT1B/1D/1F agonist) a synthetic ergotamine has fewer side effects than previously used ergotamines and is dosed parenterally.[78] It has been shown to be effective early or late in a migraine attack, especially in patients who have not responded to triptans.[78] Due to its variable availability across different countries, the prescribing guidelines differ from country to country.[79-82]

Ditans

Ditans are selective 5-HT1F receptor agonists acting on the trigeminal system. However, because of their low affinity for 5-HT1B, they receptors do not cause vasoconstriction.[83] The absence of vasoconstriction makes them particularly useful for patients who responded well to triptans but later developed vascular contraindications.[84] Lasmiditan is dosed once in 24 h and at doses of 50 mg, 100 mg and 200 mg has shown 2-h pain freedom rates were between 28% and 39%[83] A year long safety study evaluating up to four doses of Lasmiditan per month for acute attacks showed only mild side effects with its use such as sedation, dizziness, paraesthesias, and fatigue.[85] However, due to its sedating effect, patient are usually advised to avoid driving at least for 8 h after taking Lasmiditan.[65,85]

Gepants

As mentioned earlier CGRP plays an important role in migraine pathophysiology and blocking its activity can abort a migraine attack.[57] Two CGRP receptor antagonists (called gepants) are FDA approved for the acute treatment of migraine in adults: ubrogepant and rimegepant.[65,66] Ubrogepant is dosed as needed for migraine, with an additional dose as needed in 2–24 h while rimegepant is dosed once a day.[86-88] Side effects are nausea, somnolence, and dry mouth for ubrogepant and nausea and hypersensitivity reactions for rimegepant.[87,88] CGRP antagonism does not cause vasoconstriction, theoretically making it safe to use in people with stable cardiovascular disease,[89] however studies advice for cautious use in patients with significant cardiovascular risk factors.[90] Intranasal zavegepant 10 mg and 20 mg has been found to be effective for the acute treatment of migraine, with a favorable safety profile.[91] Gepants are one class of drugs that do not cause medication overuse headache and are now

being evaluated for preventive treatment.[65,66] Two very recent studies have found the role of rimegepant[92] and atogepant[93] for prophylactic treatment of migraine quite promising.

PREVENTIVE THERAPY

Studies have consistently shown that patients report reduced disability and improved quality of life with effective preventive treatment.[94] The goal of preventive medication is to reduce the overall burden and disability of migraine. An effective preventive medication reduces the severity or duration of headache attacks, reduces the need for acute treatment, and improves the efficacy of acute treatments. A reduction in headache frequency of 50% or more is considered a good response to treatment.[94] Beta-blockers, antiepileptics, antidepressants, ACEIs, ARBs, calcium channel blockers, and CGRP antibodies are presently used for the preventive treatment of migraine.[79-82,94] A brief summary of various guidelines is given in Table 4.

Monoclonal antibodies

Monoclonal antibodies targeting the CGRP receptor are the latest addition to the growing armamentarium of migraine treatment.[61,95] On an average the 50% responder rate for the monoclonal antibodies is around 50–60%.[96] The four approved CGRP antibodies are eptinezumab (100–300 mg IV every 3 months), erenumab (70 or 140 mg SC monthly), fremanezumab (225 mg SC monthly or 675 mg SC every three months), and galcanezumab (240 mg loading dose then 120 mg SC monthly).[97] The recently published EMPOwER study established the efficacy and safety of Erenumab in adults with episodic migraine from Asia, the Middle East, and Latin America.[98]

Neuromodulation

Pharmacological treatment can cause unacceptable side effects, have limited efficacy, abuse potential and in some cases can lead to medication overuse headache. For such patients, the non-invasive neuromodulation devices can be offered.[94] FDA has approved external trigeminal nerve stimulation,[99] single-pulse transcranial magnetic stimulation,[100] non-invasive vagus nerve stimulation,[101] and remote electrical neuromodulation[102] for the treatment of acute migraine attacks. These devices are believed to act through the modulation of peripheral or central pain pathways and are placed against the skin.[103] Proportions of patients achieving pain freedom at 2 h, a standard recommended endpoint for acute treatment of migraine has been variable with different neuromodulatory devices, being about 40% for vagus nerve stimulation as compared to around 20% with sham stimulation.[101] The

Table 4 Preventive treatment of migraine

Drug (Daily dose in mg)	IAN[79]	AHA[95]	EHF[81]	CHS[82]
Propranolol (80-160mg)	Recommended	Established effective	Recommended	Strong recommendation High quality evidence
Metoprolol (50-100mg)	Recommended	Established effective	Recommended	Strong recommendation High quality evidence
Atenolol(25-100mg)	Recommended	Not mentioned	Recommended	Not mentioned
Sodium valproate (600-1500mg)	Recommended	Established effective	Recommended	Weak recommendation High quality evidence
Topiramate (50-100mg)	Recommended	Established effective	Recommended	Strong recommendation High quality evidence
Amitriptyline (10-100mg)	Recommended	Probably effective	Recommended	Strong recommendation High quality evidence
Venlafaxine (75-225mg)	Not mentioned	Probably effective	Not mentioned	Weak recommendation Low quality evidence
Flunarizine (5-10mg)	Recommended	Not mentioned	Recommended	Weak recommendation High quality evidence
Verapamil (120-240mg)	Not mentioned	Inadequate data	Not mentioned	Weak recommendation Low quality evidence
Candesartan (8-16mg)	Not mentioned	Possibly effective	Recommended	Strong recommendation Moderate quality evidence
Gabapentin (900-3600mg)	Not mentioned	Inadequate data	Not mentioned	Strong recommendation Moderate quality evidence
CGRP Monoclonal antibodies[1]	Not mentioned	Not mentioned	Recommended	Not mentioned
Onabotulinum toxin A 155U S/C monthly	Not mentioned	For chronic migraine	For chronic migraine	For chronic migraine

IAN: Indian Academy of Neurology; AHS: American headache society; EHF: European headache federation CHS: Canadian headache society

adverse event profile is mostly device related and has so far been found to be acceptable.

Other/alternative treatment modalities for migraine

Nonpharmacologic treatments, including lifestyle modifications[104] (adequate and quality sleep, proper hydration, well-balanced meals, minimizing alcohol and caffeine and participating in regular physical activity); behavioral and mind-body treatments[105,106] (cognitive-behavioral therapy, relaxation training); herbal and nutritional supplements[107-109] (magnesium, riboflavin, Vitamin D, Coenzyme Q10, feverfew, and butterbur); and physical treatments[110,111] (massage, acupuncture, cold therapy, osteopathic manipulation, yoga) are now an important component of the migraine treatment plan. The evidence for their efficacy in migraine is continuing to grow.

TREATMENT OF CHRONIC MIGRAINE

Several oral treatments have been studied for chronic migraine. Although amitriptyline, gabapentin, sodium valproate, and the muscle relaxant tizanidine have been reported to have some efficacy, topiramate alone has a high level of evidence.[66] Trials evaluating the effectiveness of CGRP monoclonal antibodies in chronic migraine have been positive and all of them are considered good treatment options.[65,66] Onabotulinumtoxin A has Level A evidence for the prevention of chronic migraine.[80,81] There is some evidence to suggest that CGRP antagonism and onabotulinumtoxin A may be synergistic and the two can be used in combination.[65] Even though the technique and frequency of administration aren't yet standardized, greater occipital nerve (GON) block has been found to significantly reduce pain intensity and analgesic medication consumption in patients with chronic migraine.[112,113]

MIGRAINE DURING CORONA VIRUS DISEASE-19 (COVID-19) PANDEMIC

A recent review looked at the management of migraine patients during the covid times and pointed out that factors such as forced social isolation, lack of easy access to healthcare, persistent stress and anxiety, disturbances of the daily routine, and uncertainty about future have made life difficult for migraine patients.[114] Another web-based survey found increase in the frequency of migraine attacks, greater analgesic abuse, and propensity of migraine chronification and loss of earlier obtained therapeutic response during the present pandemic.[115] Contrarily, few studies from Italy[116] and the Netherlands[117] have found improvement in migraine during the lockdown in pandemic times. It has been universally suggested that telemedicine and Internet based consultations should be a rule in the present times.[114,115] Patients should be made aware of red flags suggesting headaches other than migraine. Overall, the drugs for acute and chronic treatment remain the same as during the non-covid times, but accessibility to drugs could be an issue. So, an adequate supply of medications must be ensured and the patient should maintain strict compliance to avoid breakthrough headaches due to missing the drugs. The importance of non-pharmacological treatment especially yoga, behavioral, and mind-body treatments can not be overemphasized in the present times.

CONCLUSION

In the past few decades, there have been significant advances in our understanding of migraine. The vascular theory which held strong for all these years has largely been debunked and migraine is now considered a disorder of central information processing. The pathophysiology is now better understood and is described separately for the five different phases of migraine. The treatment front has seen significant advances as well. The inclusion of gepants, ditans, and CGRP antagonists, monoclonal antibodies against CGRP receptor or ligands, and neuromodulation has only widened the spectrum of migraine therapeutics. It is expected that the future migraine management will be a lot easier, patient–specific and rewarding.

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