REVIEW

Multimodal Migraine Management and the Pursuit of Migraine Freedom: A Narrative Review

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ABSTRACT

Migraine is a neurologic disease with a complex pathophysiology that can be controlled with current treatment options but not cured. Therefore, treatment expectations are highly variable. The concept of migraine freedom was recently introduced and can mean different things, with some, for example, expecting complete freedom from headache and associated symptoms and others accepting the occasional migraine attack if it does not impact functioning. Therefore, migraine management should be optimized so that patients can have the best opportunity to achieve their optimal treatment goals. With migraine freedom as a goal and, given the complex pathophysiology of migraine and the high incidence of comorbidities among individuals with migraine, treatment with a single modality may be insufficient, as it may not achieve migraine freedom in those with more frequent or disabling attacks. In this clinical perspective article, we have identified four key, partially overlapping principles of multimodal migraine treatment: (1) manage common comorbidities; (2) control modifiable risk factors for progression by addressing medication and caffeine overuse; (3) diagnose and treat secondary causes of headache, if present; and (4) individualize acute and preventive treatments to minimize pain, functional disability, and allodynia. There are many barriers to pursuing migraine freedom, and strategies to overcome them should

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be optimized. Migraine freedom should be an aspirational goal both at the individual attack level and for the disease overall. We believe that a comprehensive and multimodal approach that addresses all barriers people with migraine face could move patients closer to migraine freedom.

Keywords: Drug targeting; Expert opinions; Migraine disorders; Multimodal treatment

Key Summary Points
The meaning of migraine freedom varies among individuals with migraine and health care providers.
There are many barriers to pursuing migraine freedom, and strategies to overcome them should be optimized.
A comprehensive and individualized approach is needed to fully address risk factors and comorbidities associated with migraine.
Implementation of a multimodal management approach that addresses all barriers people with migraine face could move patients closer to migraine freedom.

INTRODUCTION

Migraine is a highly prevalent, chronic neurologic disease characterized by recurrent attacks of headache and associated symptoms [1]. Many with migraine experience less than 4 monthly headache days (MHDs) [2] and may be able to achieve adequate control of their migraine attacks with monotherapy. However, consistent with other chronic diseases with intermittent attacks, monotherapy with an acute migraine treatment may not be sufficient for patients to achieve their treatment goals, especially in those with frequent, disabling attacks. High-frequency episodic migraine (EM) and chronic migraine

(CM) often need a more aggressive treatment approach and can be particularly challenging to treat, as the attacks can be refractory to multiple individual treatments [3]. The key principles below are recommended for those who cannot achieve their treatment goals with monotherapy, such as patients with high-frequency EM, CM, and/or refractory migraine attacks.

Effective management for migraine includes acute treatments at the time of an attack and preventive treatment when warranted based on attack frequency and disability [4]. Although the goals for adequate acute and preventive treatments have been formalized (Table 1) [4–6], there is a lack of consensus regarding the long-term goals of using combination treatment for migraine management. The pursuit of migraine freedom has recently been proposed as a long-term aspirational goal for treatment [7]. To best conceptualize this pursuit, we first need to distinguish between goals for the medical field and goals for individual patients. For the field, we seek to develop a therapeutic armamentarium that makes migraine freedom possible for most patients in a manner analogous to the aspirational goal in epilepsy. Patient goals for treatment will depend on individual preferences (e.g., tradeoffs between therapeutic benefits and side effects, willingness to use injectable therapies) and the realities of what might be therapeutically possible. Overall, the approach needs to be one that optimizes benefits and minimizes harms for each patient.

The definition of migraine freedom varies among individuals with migraine and health care providers (Fig. 1). Some characterize migraine freedom as freedom from disability and interictal fear or anticipatory anxiety, while others aspire to complete freedom from headache pain and associated symptoms. A key step in the pursuit of migraine freedom is the achievement of migraine control, meaning that the individual has effective tools to manage the impact of their migraine attacks rather than feeling that their migraine disease controls them.

Additionally, the definition of migraine freedom can change for individuals over time, depending on their response to treatment. Complete freedom from all symptoms of migraine remains an aspirational goal and is a

Table 1 Goals of acute and preventive treatment of migraine

Goals of pharmacologic acute treatment [4, 6]	Goals of preventive treatment [4]
• Provide rapid and consistent freedom from pain and associated migraine symptoms without recurrence	• Reduce attack frequency, severity, and duration as well as the accompanying disability
• Restore the ability to function	• Improve the response to acute treatment; improve function and reduce disability
• Minimize repeat dosing or the use of rescue medications	• Reduce reliance on suboptimal treatments
• Optimize self-care and reduce further health care resource utilization	• Reduce costs
• Minimize or avoid side effects of treatment	• Enable people to manage their own disease
	• Improve health-related quality of life (HRQoL)
	• Reduce headache-related distress and psychological symptoms

particular challenge for people with CM. The first milestone may be a reduction in headache frequency and intensity with a reduction in functional disability or impact, and once that goal is achieved, the second goal could be to move closer to freedom from the entire migraine attack. Those managing migraine should work with those with migraine to continuously improve their management depending on their responses, suggesting a dynamic process that evolves over time.

The objectives of this review are to provide an overview of the common barriers to migraine freedom and highlight the need to consider a multimodal approach to acute and preventive treatment in patients with migraine, with a specific emphasis on managing risk factors, comorbidities, secondary headache disorders, medication overuse issues, and medications that can reduce both peripheral and central sensitization. We first present a framework based on the

important role allodynia plays as a manifestation of peripheral sensitization of nociceptors and central sensitization of primary afferents. This framework can serve as a predictor of treatment response and the potential progression of migraine. We then propose a multimodal approach to provide a comprehensive plan for managing migraine. A rational approach should guide the selection of treatments based on four key principles of this rational multimodal management approach: (1) manage common comorbid conditions, (2) control modifiable risk factors for progression by addressing medication and caffeine overuse, (3) diagnose and treat secondary causes of headache, if present, and (4) individualize acute and preventive treatments to minimize pain, functional disability, and allodynia (Fig. 2). Notably, we acknowledge that there is a degree of overlap among these principles, but the basic framework may be helpful to clinicians and researchers. This article is based on clinical expertise as well as previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. A narrative review was performed after a series of detailed point-by-point discussions within the Migraine Innovation Navigation and Discovery conference. Conceptual strategies were also considered and discussions were also had via teleconferencing and email correspondence. The discussions explicitly addressed the subject content, reviewed organizational strategies, and addressed details of the narrative review.

Compliance with ethics guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## CENTRAL SENSITIZATION, ALLODYNIA, AND IMPLICATIONS FOR MIGRAINE TREATMENT

A brief review of central sensitization in migraine is needed to better understand this
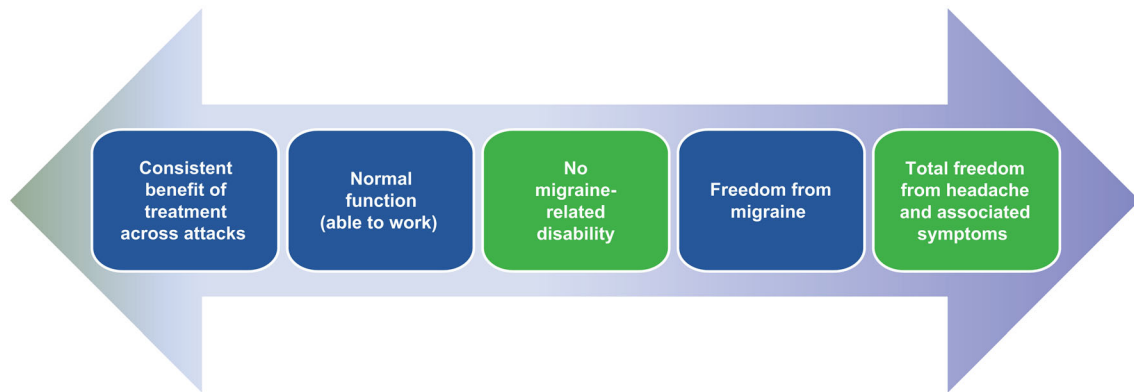
Fig. 1 The spectrum of definitions of migraine freedom

perspective for migraine management. Sensitized trigeminal afferents stimulate the trigeminocervical complex (TCC) with increasing intensity during migraine, which causes central sensitization and the amplification of pain sensations [8]. The sensitization theory of migraine attributes the persistence and frequent occurrence of migraine attacks to a lowering of the threshold of activation of pathways involved in migraine attacks that can also promote migraine progression [8]. Many factors contribute to the progression of migraine and the development of central sensitization, presenting barriers to the pursuit of migraine freedom. These include comorbid conditions, acute medication overuse, secondary causes of headache, and other risk factors for progression (Fig. 3). The impact of these factors on central sensitization requires further clarification. There are numerous neural pathways, neuropeptides, and neurotransmitters involved in migraine [9], and comorbidities can influence
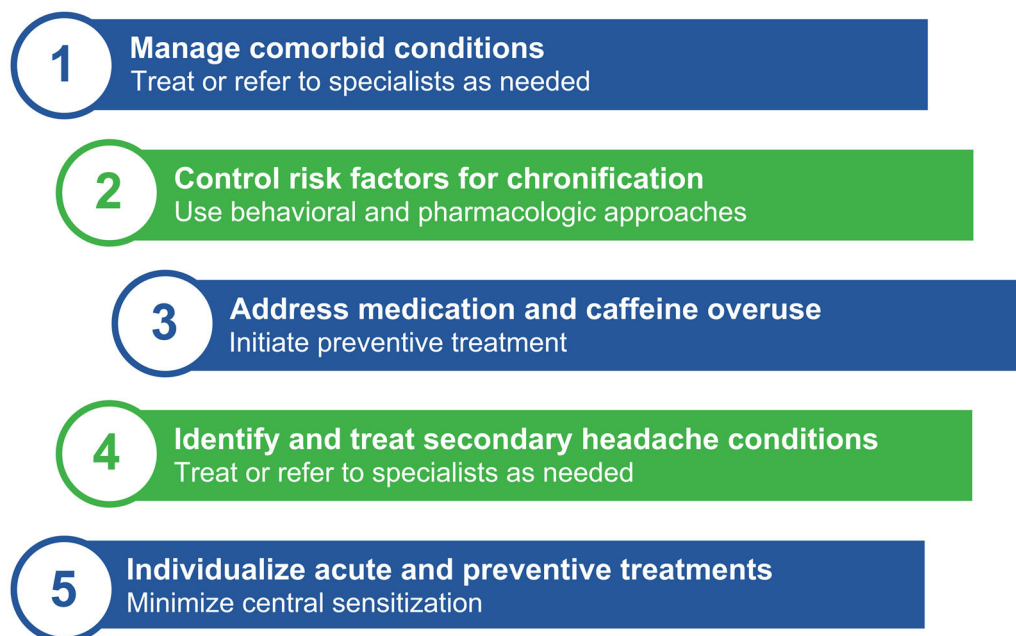

Fig. 2 Principles of rational multimodal migraine management. These principles are not meant to be mutually exclusive due to the substantial overlap and interactions between them

the expression of this disease. Since these obstacles to migraine freedom are interrelated, failing to address any individual barrier can further potentiate sensitization and increase the migraine attack frequency, which can result in disease progression (i.e., each migraine attack makes it easier to proceed into the next attack). Any management strategy with the goal of total migraine freedom must identify and address, as much as possible, the potential contributing factors to sensitization and risk factors for disease progression.

Cutaneous allodynia is considered to be a measurable clinical surrogate for central and peripheral sensitization [8, 10, 11] and is common during migraine attacks, being reported by approximately 40% to 80% of people with migraine [10, 12–15]. Additionally, the prevalence of interictal allodynia is higher in CM than in EM, which suggests ongoing sensitization between migraine attacks [16, 17]. Notably, triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and other acute treatments may be less effective in patients with cutaneous allodynia [18–21]. One such explanation for this observation is that when allodynia develops, the second-order neuron can become autonomously active [18]. Another proposed explanation is the absence of $5HT_{d1}$ receptors on the second-order neuron following the development of allodynia [18]. The potential impact of effective migraine-specific preventive treatments on allodynia is not yet fully known, but there is preliminary evidence suggesting that some preventive medications are effective in patients with allodynia [22, 23]. Both onabotulinumtoxinA and erenumab have demonstrated efficacy in patients with migraine with allodynia [22, 23]. The pathogenic mechanisms by which these drugs are effective can only be hypothesized. Further research is required to confirm the pathogenic mechanisms by which these drugs are effective in patients with migraine experiencing allodynia. Additionally, the absence of allodynia has been shown to be predictive of treatment response in CM [24]. Ideally, migraine treatments should inhibit central sensitization [8] because frequent migraine attacks with long durations can lead to increased allodynia, presumably reflecting increased central sensitization [25]. An observational study demonstrated that suboptimal acute treatment is associated with an increased risk of progressing from EM to CM [26]. The authors of this study suggested that effective acute treatment shortens headache attacks and minimizes the time that the brain is exposed to migraine, potentially preventing the emergence of sensitization and disease progression [26]. Notably, using opioids to treat migraine is associated with an increased risk for allodynia [27]. Additional risk factors for developing allodynia include frequency of MHD, depression and anxiety symptoms, headache intensity, migraine severity, and medication overuse [28]. However, the relationship between
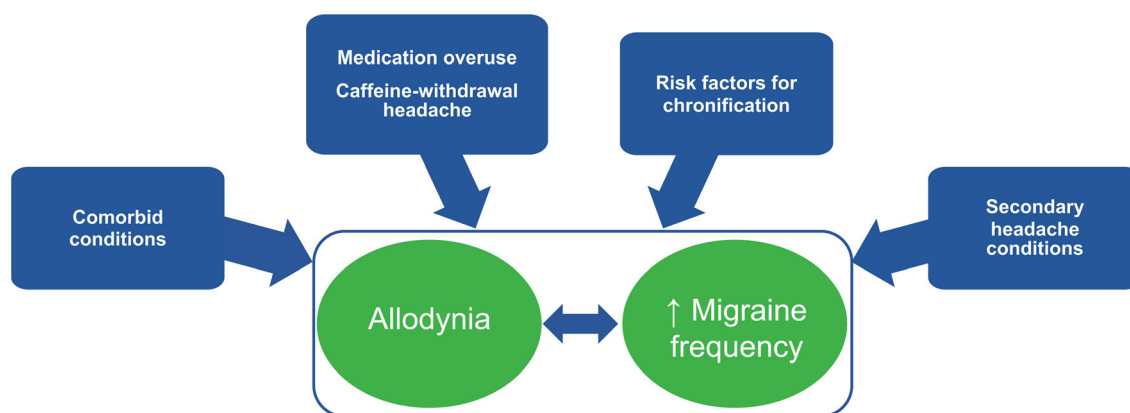
Fig. 3 Barriers to achieving migraine freedom. These concepts have the potential to overlap and interact with each other and serve as concurrent barriers to migraine freedom

allodynia and medication overuse is bidirectional, since allodynia has also been shown to increase the risk for medication overuse [14]. Other comorbid conditions and risk factors for progression that further potentiate central sensitization should also be addressed, as discussed in the next section.

Based on our review of this body of evidence, it may be likely that partially addressing factors that contribute to headache may not fully attenuate central sensitization and, therefore, may be insufficient to provide migraine control. We also suggest that in CM patients, every headache likely has features of migraine. While some attacks may have a greater intensity than others, the risk of sensitization may be present with all attacks. This scenario may therefore indicate a need to treat all attacks while still avoiding medication overuse. Based on the proposed model of medication overuse headache, which involves cutaneous allodynia or latent sensitization, the gepant class does not lead to the development of medication overuse headache while providing preventive benefits [29]. However, treatment with gepants may not be possible for situations in which gepants are not available or are prohibitive in terms of cost. Caution should also be taken when treating with medications that confer a risk of developing medication overuse headache.

MULTIMODAL MIGRAINE MANAGEMENT

Management of Comorbid Conditions

Management of comorbid conditions is the first principle to address as a barrier to obtaining migraine freedom because of the high frequency of comorbidities in this population. In the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study, 92.4% of participants with migraine reported at least one comorbidity [15]. Results from the Migraine in America Symptoms and Treatment (MAST) Study showed that, compared with people without migraine, those with migraine were twice as likely to have peripheral artery disease, angina, allergies/hay fever, epilepsy, arthritis,

rheumatoid arthritis, asthma, and vitamin deficiency, and three times more likely to have insomnia, depression, anxiety, and gastric ulcer or gastrointestinal bleeding [30]. Importantly, the number of comorbidities, certain types of comorbidities (e.g., psychiatric), and combinations of comorbidities (e.g., pain and respiratory) increase the likelihood of progression from EM to CM [31].

Depression is frequently comorbid with migraine, and the proportion of people with comorbid depression increases with the frequency of migraine attacks [32–34]. Depression is one of the most impactful comorbidities of migraine, which, together with anxiety, contributes significantly to increased disability and impaired health-related quality of life (HRQoL) [35, 36]. In a longitudinal study, depression demonstrated a dose-dependent prediction for progression from EM to CM [37]. Anticipatory anxiety may also be a factor in medication overuse, since people may feel prompted to take acute treatments too early or frequently [35]. Catastrophizing and anticipatory anxiety play a significant role in the health behaviors of people with migraine and are associated with a poorer treatment response [38]. Levels of disability are higher in persons with comorbid migraine and depression or anxiety and higher still in persons with both depression and anxiety at any level of monthly headache day frequency [39]. In addition, there is a genetic overlap between depression, anxiety, and migraine, suggesting a biological relationship between migraine and psychiatric conditions [40]. Notably, many medications currently used for preventive treatment of migraine have antidepressant and anxiolytic properties.

Noncephalic pain and fibromyalgia are painful conditions that are also associated with migraine [41, 42]. Noncephalic pain may also be associated with migraine progression [41]. Those with both CM and comorbid noncephalic pain are less likely to remit than those without noncephalic pain [41]. Among individuals with migraine, comorbid fibromyalgia is associated with increased headache-related disability, depression, and headache severity compared with those without fibromyalgia [43]. Patients with chronic pain might also use analgesics to

manage these conditions, which can lead to medication overuse headache. Using analgesics for noncephalic pain can generate medication overuse headache in those with migraine regardless of what these medications are being taken to treat [44]. Pain disorders and/or their treatment with medications may activate overlapping pain mechanisms contributing to central sensitization [20, 41, 42].

Addressing sleep disorders and improving overall sleep quality is important for migraine management because appropriate sleep is essential for the regulation of a wide range of homeostatic functions. Migraine attacks may disrupt sleep, and sleep disorders may lower pain threshold and exacerbate migraine [45]. Several studies demonstrated that poor sleep quality may predict onset or exacerbation of migraine [45–48]. Sleep disorders related to migraine can include but are not limited to habitual snoring, sleep apnea, insomnia, circadian rhythm (i.e., sleep–wake) disorders, and sleep movement disorders [49, 50]. Results of the CaMEO study showed that—compared with the reported general prevalence estimates of sleep apnea, which range from 9 to 38% [51]—those with migraine, especially CM, had an increased risk for and a potential underdiagnosis of sleep apnea and sleep disturbances. Among individuals with migraine, sleep apnea is more prevalent among men than women [45]. Study results found that respondents with EM and CM who screen positive for a high risk for sleep apnea more commonly experience their most severe headaches around the time of awakening and in the morning [45]. More studies are needed to determine the impact of improving sleep quality/treating sleep disorders on migraine progression, but even with the lack of substantial data, clinical experience suggests that insufficient or inconsistent sleep cycles can impact the quality of life for those with migraine and should be addressed in the pursuit of migraine freedom.

In the CaMEO study, latent class models were used to identify eight groups of patients based on comorbidities that tended to occur in people with migraine [15]. In comparison to the class with the fewest comorbidities, the class with the most comorbidities was more than five

times more likely to progress to CM [31]. In this study, classes were defined based on respiratory, psychiatric, pain, and cardiovascular comorbidities in various combinations. The plausible mechanisms that may link migraine progression involve the mechanisms of the comorbidities, including inflammation from pain and respiratory comorbidities, and alterations in neurotransmitter systems for psychiatric comorbidities. Although comorbidities are associated with migraine progression, there is only limited evidence that treating comorbidities improves outcomes. The evidence is probably strongest for obesity treatments (i.e., bariatric surgery, behavioral weight loss) [52, 53].

Modifiable Risk Factors for Migraine Progression

Risk factors for progression are classified as either modifiable or nonmodifiable [54]. Nonmodifiable risk factors typically include gender, age, and race and are important to recognize, but, since they cannot be changed, clinicians focus more on modifiable risk factors in order to reduce risk of progression. Modifiable risk factors include some comorbidities (e.g., depression, obesity), stress, frequent attacks of long duration, caffeine intake, medication overuse, and sleep quality [54]. As with defining individualized patient goals, it is appropriate for those managing migraine to identify patient-specific modifiable risk factors to personalize care. Medication overexposure and caffeine intake are recognizable and frequent modifiable risk factors that should be addressed when present.

Many clinic-based and population-based studies suggest that symptomatic medication overexposure with some acute treatments is associated with increased migraine severity and progression from EM to CM [55]. Medication overexposure is also associated with poor health-related quality of life (HRQoL) and high levels of disability [56, 57]. This association is particularly strong for individuals who use opiates and barbiturates [55, 58]. In a cross-sectional observational study, those with the most

severe migraine disease and most frequent headaches were most likely to be overusers of NSAIDs (at least 15 days/month), ergots (at least 10 days/month), and opioids/barbiturates (at least 10 days/month) [56, 59, 60]. This association is also described with triptan use [60]. Medication overuse headache is a clinical diagnosis describing when the headache is directly associated with medication overexposure; it is associated with distinct changes in the meso-cortical-limbic circuit and the orbitofrontal cortex, which can be reversed with successful treatment [61]. Even if medication overexposure does not result in medication overuse headache, end organ damage related to overuse (e.g., analgesic nephropathy, liver toxicity, and peptic ulcer disease) may occur, so acute medication overexposure should be avoided. Medication overexposure can also lead to decreased effectiveness of other treatments. For example, acute medications that contain barbiturates may interact with metabolic pathways for the gepants, potentially making these medications less effective [62].

Caffeine can both relieve and trigger migraine attacks [63] and was a risk factor for chronic daily headache in a population-based case–control study [64]. Caffeine is used as an adjuvant to analgesics for headache, and over-the-counter combination medications containing caffeine are often used to treat migraine [65]. Unfortunately, even relatively low-dose caffeine consumption (100 mg/day) can lead to withdrawal effects (including headache) when discontinued [66]. Notably, complete withdrawal of nonmedication caffeine (e.g., coffee-containing drinks) may improve response to acute treatments for migraine [67]. People with sleep problems may be at risk for caffeine overuse. Medication and caffeine overuse should be evaluated and addressed in individuals so that migraine freedom can be achieved.

Secondary Causes of Headache

Secondary causes of headache may also present barriers to the pursuit of migraine freedom. Many factors can give rise to intractable headache with migraine-like features. Medication overuse headache and post-traumatic headache [68] are secondary headache disorders that can also be causes of secondary headaches in primary headache disorders. For example, infectious illnesses including meningitis, arterial dissection, subarachnoid hemorrhage, and stroke are all associated with onset of headache or a transformation to a more severe chronic headache form that may have migraine features. Categories of secondary headaches in the *International Classification of Headache Disorders, 3rd edition* (ICHD-3), include headaches attributed to trauma or injury to the head and/or neck; cranial and/or cervical vascular disorder; nonvascular intracranial disorder; a substance or its withdrawal; infection; a disorder of homeostasis; a disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure; and psychiatric disorder [1]. These secondary causes may exhibit symptoms similar to migraine and may also serve as factors that exacerbate an underlying primary headache disorder or activate headaches in genetically predisposed individuals. A first step in management in these scenarios is to diagnose the primary headache disorder and to identify and treat underlying factors that may exacerbate the underlying disorder. Potential secondary causes of headache must also be evaluated and often require consultation with a specialist. Below are a few types of secondary headaches and additional causes of headache that should be considered.

Cervicogenic headaches are difficult to identify and may require consultation with a pain specialist for treatment; a simplified diagnosis of either migraine or cervicogenic headache in an individual who has both will likely lead to inadequate treatment [69]. Cervicogenic headache is a secondary headache that is a distinct entity from migraine but also involves pain in the trigeminal system [70]. Diagnosing cervicogenic headache is challenging, as clinical features such as unilateral headache, nausea, photophobia, phonophobia, and neck pain may overlap with symptoms of migraine [69]. However, if there is a cervicogenic component to a person's headache, both the cervicogenic and migraine components may need to be treated in order to achieve a headache-free state.

Similarly, consultation with a specialist may be required for individuals with cervical spine pathology, increased intracranial pressure, or cerebrospinal fluid (CSF) leaks. Idiopathic intracranial hypertension (IIH) can be comorbid with migraine. A case–control study showed the odds of having migraine was seven times higher in people with IIH compared with controls [71]. While IIH is considered neither necessary nor sufficient to drive migraine progression, it is likely to be a modifiable risk factor for progression [72]. CSF pressure is clinically independent from headache in those with IIH [73]. One mechanism postulated for the relationship between IIH and migraine is that trigeminal activation may be driven by elevated CSF pressure. The elevated CSF pressure observed in IIH could thus lead to persistent trigeminal activation and sensitization. Central sensitization from migraine could, alternatively, contribute to the development of IIH [73].

Individualizing Acute and Preventive Treatments by Linking Pathophysiology to Migraine Treatment

Effective multimodal management of migraine requires an understanding of the pathophysiology of migraine and how acute and preventive treatments target these different physiological pathways. A lowered threshold for migraine may result from dysfunction in the nociceptive system [8, 74]. Briefly, activation and sensitization of trigeminal sensory afferents in the periphery (i.e., dural and meningeal trigeminal nociceptors) result in repeated signals of increasing intensity to the brainstem, which leads to central sensitization and further amplification of the pain (reviewed by Pietrobon and Moskowitz [75]) [8]. Sensory neurons of the trigeminal ganglion synapse with second-order neurons in the trigeminal nucleus caudalis (TNC) in the brainstem and have collateral terminals in the spinal trigeminal nucleus and upper cervical spinal cord [8, 76]. Central sensitization leads to abnormal neuronal excitability in the TNC that decreases the threshold for generating the next migraine attack [8, 77]. Convergence of meningeal nociceptors and extracranial primary afferents for the upper cervical roots in the spinal TCC may contribute to the perception of periorbital and occipital pain [76]. Projections of spinal trigeminal nucleus neurons ascend into the parabrachial area, hypothalamic areas, preoptic nuclei, and thalamic nuclei. Dura-sensitive neurons from the thalamic nuclei project to somatosensory cortices and cortical areas of motor, parietal association, retrosplenial, somatosensory, auditory, visual, and olfactory cortices. The hypothalamus is anatomically connected to the spinal trigeminal nucleus and may contribute to central sensitization. Descending neuronal pathways from somatosensory and insular cortices, hypothalamus, periaqueductal gray matter, and nucleus cuneiformis also modulate the activation and sensitization of the spinal trigeminal nucleus [76, 78]. Data from rat models suggest that central sensitization depends on the barrage of signals from meningeal nociceptors and impaired descending inhibition of pain and/or the enhancement of descending pain-facilitating processes from the rostral ventromedial medulla [79]. Neuroimaging evidence suggests that the functional connectivity between the hypothalamus, midbrain (periaqueductal grey and dorsal pons), and thalamus is altered in the premonitory stages of migraine before the appearance of headache [77, 80–82]. The occurrence of aura and associated cortical spreading depression/depolarization (CSD) may trigger headaches in some individuals by activating trigeminal nociception [75, 83]. A sterile neurogenic inflammation may contribute to the sustained activation and sensitization of meningeal afferents during migraine attacks, but the processes that drive neurogenic inflammation are poorly understood [75]. This inflammation is associated with the release of vasoactive proinflammatory neuropeptides such as calcitonin gene-related peptide (CGRP) [75].

The identification of peripheral and central pathways associated with migraine, including trigeminal, cortical, subcortical, and descending inhibitory pathways, provides diverse physiological targets for therapeutic intervention. Activation of the trigeminal nerve and

trigeminal nucleus may be decreased by migraine treatments that target the action of CGRP. CGRP is released from trigeminal fibers that innervate dural arteries and possibly the trigeminal ganglion [84]. Currently approved medications that target CGRP or its receptors include small-molecule gepants (ubrogepant, atogepant, zavegepant, and rimegepant) and four monoclonal antibodies (mAbs; erenumab, galcanezumab, fremanezumab, and eptinezumab) [85, 86]. The anti-CGRP agents appear to exert most of their inhibitory effect on central sensitization by blocking peripheral CGRP-ergic neurotransmission and thereby reducing peripheral sensitization [86]. A preclinical study demonstrated that CGRP-targeted mAbs prevent sustained trigeminal firing by preventing the activation of CGRP receptors on thinly myelinated Aδ-fiber nociceptors [87]; a similar preclinical study of atogepant demonstrated that it reduced the activation of C-fiber nociceptors early and briefly, which was followed by a delayed and more sustained prevention of Aδ-fiber nociceptors [88]. Additionally, neuroimaging evidence suggests that CGRP-targeted mAbs and small-molecule gepants may also indirectly or directly modulate the functional connectivity of the hypothalamus with other brain regions to alter brain processing of trigeminal nociceptive input [88, 89].

OnabotulinumtoxinA, an approved preventive treatment for CM [90], inhibits peripheral sensory nerve endings of trigeminal and cervical ganglia neurons by blocking the fusion of synaptic vesicles with the nerve membrane [91]. Inhibiting vesicle fusion prevents synaptic release of neurotransmitters and neuropeptides, such as substance P, glutamate, and CGRP, as well as the insertion of receptors and ion channels, such as TRPV1 channels, into nociceptive nerve terminals [91]. The effectiveness of onabotulinumtoxinA in CM is theorized to be mediated at multiple points in pain activation pathways, including downregulating receptors on nociceptive neurons and reducing the availability of neurotransmitters and neuropeptides for activating pathways involved in migraine [91–94]. In preclinical studies, onabotulinumtoxinA reduced sustained firing of unmyelinated C-fiber nociceptors [95].

Many studies suggest a potential role for glutamate in migraine. Glutamate, an excitatory neurotransmitter, is present in high concentrations in all thalamic nuclei that contain trigeminovascular neurons [9]. Glutamate has multiple receptors, and the activation of metabotropic glutamate receptors may prime ionotropic glutamate receptors to enhance their excitability, a process that has been postulated to contribute to central sensitization [96]. Glutamate may also play a role in CSD [96]. The antiepileptic medications gabapentin, pregabalin, and topiramate target glutamate receptors on presynaptic excitatory neurons [97]. Of these, only topiramate is approved for the prevention of migraine. Topiramate may exert its effects on migraine pain by modulating nociceptive processing in thalamocortical networks [98].

Serotonin is also implicated in migraine pathophysiology. Axons producing serotonin (5-hydroxytryptamine [5-HT]) are found at high density in all thalamic nuclei that contain trigeminovascular neurons [9]. The 5-HT$_1$ subfamily (subtypes 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1F}$) is most frequently implicated in migraine [99]. 5-HT$_1$ agonists currently approved for the acute treatment of migraine include ergot alkaloids and triptans, which target 5-HT$_{1B/1D}$, and lasmiditan, which targets 5-HT$_{1F}$ [1, 5]. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), may have some efficacy for the prevention of migraine, whereas selective serotonin reuptake inhibitors (SSRIs) do not [100, 101].

Pituitary adenyl cyclase-activating polypeptide (PACAP)-38 and PACAP-27 can induce migraine-like attacks in people with migraine when infused intravenously and may have a role in migraine pathophysiology [102–104]. PACAP may modulate nociceptive neurologic circuits and regulate the production of inflammatory mediators. Moreover, in vitro studies suggest PACAP-38-positive cells occasionally express vasoactive intestinal peptide/PACAP receptors 1. The role for anti-PACAP medications in migraine and migraine therapy is being explored.

Neuromodulatory devices are nonpharmacologic approaches for the acute and preventive treatment of migraine. These devices act by decreasing neuronal excitability in various brain regions involved in migraine, including trigeminal

nerve and thalamocortical pain pathways, as well as the cortical spreading depression associated with migraine aura [105]. Multiple noninvasive devices have been cleared by the FDA for migraine treatment, including external trigeminal stimulation (eTNS), single-pulse transcranial magnetic stimulation (sTMS), noninvasive vagus nerve stimulation (nVNS), remote electrical neuromodulation (REN), and combined occipital-trigeminal neurostimulation (CO-TNS) [5, 106, 107]. Other nonpharmacologic treatment options include behavioral therapy and nutraceuticals [108, 109]. There is evidence to support the use of behavioral therapy, and it is recommended as monotherapy or adjunctive therapy for the acute and preventive treatment of migraine [4]. Nutraceuticals could also be considered in migraine management; however, there is limited evidence to support their efficacy, safety, and tolerability.

The different pathways targeted by the available migraine treatment options speak to the multimechanistic nature of migraine pathophysiology. Combining multiple preventive treatments that target different physiological pathways may provide additional benefit compared with preventive monotherapy. Preclinical data suggest that combination treatment with a CGRP-targeted mAb and gepants with onabotulinumtoxinA is likely additive and possibly synergistic [110–115]. As noted above, the afferents inhibited by anti-CGRP medications are different from those inhibited by onabotulinumtoxinA. CGRP-targeted mAbs have been shown to prevent sustained trigeminal firing by preventing the activation of CGRP receptors on thinly myelinated Aδ-fiber nociceptors [87]. Atogepant, a gepant, prevented the activation of CGRP receptors on both Aδ- and C fiber nociceptors [88], whereas onabotulinumtoxinA reduced the sustained firing of unmyelinated C-fiber nociceptors [95, 116].

A similar rationale can be proposed for concomitant acute treatment with multiple medications that target different pathways. For example, triptan–NSAID combinations may demonstrate clinical synergy, with triptans activating $5\text{-}HT_{1B/1D}$ receptors and NSAIDs inhibiting inflammation and perhaps having central inhibitory effects as well [21, 117]. The combination of sumatriptan and naproxen was more effective in modified factorial studies than the same dose for either sumatriptan or naproxen as monotherapy [118–120]. The synergistic or additive relationship between sumatriptan and naproxen was confirmed by statistical modeling [121], a method that could be used to assess the efficacies of other migraine medication combinations. Combination treatment with an investigational medication with meloxicam and rizatriptan similarly showed promising results for the acute treatment of migraine attacks (NCT04163185), and its resubmission to the FDA for a new drug application in late 2023 is planned [122]. Several randomized, double-blind, placebo-controlled trials demonstrated the safety and efficacy of combination treatments, such as acetaminophen plus rizatriptan or naproxen plus sumatriptan, for the acute treatment of migraine [117, 123, 124].

Implementation of multimodal migraine treatment is limited by the paucity of studies evaluating combinations of treatment. For instance, randomized controlled trials (RCTs) evaluating combination treatment with a gepant or a CGRP mAb and onabotulinumtoxinA, which is used in practice, and other combinations for CM are lacking [114]. Real-world data suggest that this combination may be an effective strategy based on the mechanism of action reviewed above, but RCTs are needed to confirm these results [113, 115, 125]. Additionally, combining a preventive medication with behavioral modalities was effective for acute treatment in an RCT [126]. Because this is an evolving area of research, additional RCTs are needed to fully explore the effects of different combinations of migraine treatments.

LIMITATIONS

As this is a narrative review, a systematic literature review was not conducted. The suggestions made in this manuscript originate from the authors' clinical and research experience.

SUMMARY AND CONCLUSIONS

Migraine is a complex disease with multiple genetic, epigenetic, and environmental factors

contributing to its clinical expression [49, 127, 128]. Combination treatments are now widely used for an array of complex diseases, including cancer, infectious diseases, and neurodegenerative disorders [3, 129]. An understanding of barriers to the pursuit of migraine freedom and the implementation of a multimodal management approach have been the focus of this review because they may be necessary for achieving the best possible outcomes for individuals with migraine. Therapeutic goals for patients, clinicians, and guideline developers are based, at least in part, on achievable goals. Advances in headache medicine mandate rethinking clinical goals. Aspirational goals can inspire providers, attract resources, and help patients and providers work together toward an expanded horizon. An aspirational goal such as migraine freedom, or an immediately achievable goal such as fewer headache days, reduced disability, and improved HRQoL, requires better use of the "arrows" in our therapeutic "quiver." Multiple mechanisms predispose patients to migraine, and multiple pathways lead to migraine attacks. The multi-mechanistic nature of migraine provides a foundation for multimodal therapy that should be based on a systematic approach to making treatment decisions using predictive modeling [130]. A comprehensive and individualized approach is needed to fully address risk factors and comorbidities associated with migraine. Additional guidance on and clinical experience of rational multimodal migraine management are needed, which may vary based on the practice setting. Future research and publications should seek to expand the more individualized recommendations we have made here into more generalized recommendations that can be incorporated into guidelines, namely developing a collaborative relationship between patients and clinicians to help meet individual goals related to migraine freedom.

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