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EPISODIC MIGRAINE (S NAHAS, SECTION EDITOR)

Emerging Treatments in Episodic Migraine

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Abstract

Purpose of Review The purpose of this review is to evaluate and describe recent and emerging treatment options for episodic migraine.

Recent Findings Recent advances have been made in better understanding the pathophysiology of migraine, which has led to further investigation of potential new pharmacologic and non-pharmacologic treatment options.

Summary A number of new medications are emerging for the acute and preventive treatment of migraine, including CGRP monoclonal antibodies, CGRP receptor antagonists, serotonin 5-HT_{1F} agonists, and PACAP receptor monoclonal antibodies. Additionally, newer studies on existing non-invasive neuromodulation devices including transcranial magnetic stimulation, supraorbital transcutaneous nerve stimulation, and transcutaneous vagus nerve stimulation have recently received FDA approval for use in migraine. Neuromodulation devices including percutaneous mastoid electrical stimulation, non-painful remote electrical stimulation, and caloric vestibular stimulation are undergoing further investigation and have shown promising results thus far. These new developments are expected to contribute to better treatment and decreased disability in migraine.

Keywords Episodic migraine · Treatment · Calcitonin gene-related peptide · Neuromodulation

Introduction

Migraine is ranked as the most disabling neurologic disease and the sixth cause of disability worldwide [1, 2]. Effective management of migraine attacks rests on several key treatment principles: early intervention, adequate dose and route of abortive therapy, and co-administration of an antiemetic or pro-kinetic drug to facilitate absorption. Ideal acute migraine treatment would promptly restore a patient's ability to function by providing rapid, effective relief with only minimal or no adverse effects. However, most currently available acute and preventive drugs for migraine act on several neurotransmitters and are therefore ineffective and/or responsible for a wide range of side effects. This adds to difficulty with compliance and poor responder rates (40–50% in most studies) [3]. NSAIDs remain the most commonly used acute migraine treatment. Ergot derivatives and triptans have also been mainstay in episodic and chronic migraine; however, their vasoconstrictive effects contraindicate their use in several clinical scenarios including uncontrolled hypertension, coronary artery disease, peripheral vascular disease, stroke, impaired hepatic or renal function, and pregnancy. There is also significant risk of developing medication overuse headache with these current acute treatment options, with recommendations for acute medications in general not to exceed 10 days of use per month. Additionally, some patients with episodic migraine do not wish to use medications and would prefer alternative non-pharmacological treatment strategies.

Recent advances in the understanding of migraine pathophysiology have allowed development of new biologics, drugs, and devices that target specific mechanisms known to be active in the disorder. This targeted approach leads to improved efficacy and less unwanted side effects. In contrast to current migraine management options, which were primarily developed and licensed for disorders outside of headache, new treatments have been developed specifically for migraine based on human migraine studies, such that they may exert a more direct effect on specific migraine pathways.

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We will review these exciting emerging treatments for episodic migraine, including both pharmacologic and non-pharmacologic options.

Pharmacologic

CGRP Antagonists (Gepants)/CGRP Monoclonal Antibodies

Calcitonin gene-related peptide (CGRP) is a neuropeptide released from trigeminal nerve fibers and has been found to play a central role in the pathophysiology of migraine [4]. CGRP induces vasodilation, mast cell degranulation, and pain transmission within trigeminal pathways. Investigation has shown that CGRP is released during migraine attacks, and is persistently elevated in patients with chronic migraine. In addition, intravenous infusion of CGRP triggers symptoms identical to spontaneous migraine attacks [5].

Small molecule CGRP receptor antagonists (also known as "gepants") were shown to be efficacious in acute treatment of migraine; however, initial trials were discontinued due to findings of hepatotoxicity. Newer gepant small molecules are currently under development. In a recent phase IIb randomized, double-blind, placebo-controlled trial of a novel CGRP receptor antagonist ubrogepant (MK-1602), investigators found significant superiority of ubrogepant 100 mg over placebo for 2-h pain freedom (25.5 vs. 8.9%; $p < 0.001$) [6]. This study provided good safety and tolerability data, with no evidence of post-treatment hepatic dysfunction in any of the 527 participants who received ubrogepant.

There are currently four CGRP monoclonal antibodies under review, with the first expected to be approved in 2018. Three of these are against CGRP itself: galcanezumab, eptinezumab, and fremanezumab; and one against the CGRP receptor, erenumab. All four have been found to be superior to placebo in prevention of episodic migraine. In chronic migraine, an indirect comparison with onabotulinumtoxinA and topiramate has shown CGRP monoclonal antibodies to have similar efficacy, though as of yet there have been no direct comparisons published [7]. Studies have demonstrated no significant differences across the four drugs in terms of efficacy, and all clinical trials involving anti-CGRP medications have positively shown effectiveness in treatment of acute attacks, prevention of attack onset, or reduction in attacks [4, 8]. All four CGRP monoclonal antibodies have shown good tolerability, with few adverse events, mostly with respect to injection site reactions, no serious side effects, and high retention rates of subjects in the studies. CGRP monoclonal antibodies have not demonstrated hepatotoxicity concerns in phase II and phase III studies. However, long-term safety has not yet been established in any of the CGRP antagonist or monoclonal antibody drugs.

In a recent phase III randomized placebo-controlled trial of erenumab for episodic migraine (ARISE), patients receiving erenumab reported a reduction in monthly migraine days of −2.9 days, compared to −1.8 days with placebo ($p < 0.001$). Additionally, a 50% reduction in monthly migraine days was achieved in 39.7% of patients receiving erenumab versus 29.5% placebo ($p = 0.010$), and migraine-specific medication use was reduced by −1.2 days (erenumab) versus −0.6 days (placebo) ($p = 0.002$) [9••].

A phase IIb clinical trial of galcanezumab demonstrated similar results in efficacy for patients with episodic migraine. At doses of 120 and 300 mg, galcanezumab produced a statistically significant reduction in mean headache days at 3 months compared with placebo (−4.3 days for both doses compared to −3.4 days with placebo, $p = 0.02$). Functional impact, assessed with MSQ and HIT-6 scales, was also significantly improved in the galcanezumab group compared to that in placebo [10•].

The efficacy of fremanezumab was examined in a phase III randomized placebo-controlled trial in patients with chronic migraine. This demonstrated a reduction in average number of headache days per month of -4.3 ± 0.3 with fremanezumab administered quarterly, -4.6 ± 0.3 with fremanezumab administered monthly, and -2.5 ± 0.3 with placebo ($p < 0.001$ for both comparisons). Thirty-eight percent in the fremanezumab-quarterly group and 41% in the fremanezumab-monthly group experienced a reduction of at least 50% in the average number of headache days per month, compared to 18% in the placebo group ($p < 0.001$ for both comparisons) [11••].

Unlike their triptan and ergot predecessors, CGRP receptor antagonists and CGRP monoclonal antibodies do not have any vasoconstrictive effect and therefore may be suitable for patients with vascular disease and other conditions for which triptans and ergots may be contraindicated [5]. Additionally, the long half-life of monoclonal antibodies allows for less frequent dosing than current preventive therapies, with monthly and quarterly treatment options being studied. The lack of a need for daily dosing will likely enhance treatment adherence.

The CGRP monoclonal antibody drugs have been submitted for review by the U.S. Food and Drug Administration (FDA). Erenumab has just received approval by the FDA as of May 17, 2018, and the others are expected to be approved by late 2018/early 2019.

Serotonin 5-HT_{1F} Agonists (Ditans)

Increased plasma levels of serotonin in migraine have long been described, initially leading to development of triptans, which act as 5-$HT_{1B/1D/(1F)}$ receptor agonists [12]. 5-HT_{1F} receptors are not expressed in the vasculature, making them also more suitable for those patients with vascular disease who cannot take triptan or ergot medications. Activation of 5-HT_{1F}

receptors is felt to act through modulation of the trigeminovascular system, inhibition of CGRP release, and/or decrease in the nociceptive pathway [13]. This discovery has led to investigation of selective 5-HT_{1F} agonists. One such drug, lasmiditan, has a high selectivity for the 5-HT_{1F} receptors and has been found to act centrally on trigeminal neurons due to its ability to cross the blood-brain barrier, with no vasoconstrictive action [14].

In an ongoing phase III randomized, double-blind, placebo-controlled parallel-group study investigating lasmiditan, researchers reported that pain freedom at 2 h was 31.4% for 100 mg ($p < 0.001$) and 38.8% for 200 mg ($p < 0.001$) doses compared to 21.3% for placebo [15]. The study also showed a favorable side effect profile, with none of the 3007 trial participants discontinuing the medication due to adverse effects. An open-label trial of lasmiditan is ongoing, aimed to evaluate the safety and tolerability of long-term intermittent use of lasmiditan for acute treatment of migraine [16]. Lasmiditan is expected to come under review by the FDA in the second half of 2018.

PACAP

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide located in sensory fibers and parasympathetic fibers. In addition to functioning in vasodilatation and neurogenic inflammation, it has been found to have a pronociceptive role in the CNS, and receptors for PACAP are expressed throughout the trigeminovascular system as well as the parasympathetic sphenopalatine ganglia (SPG) [17, 18].

Clinical studies have demonstrated that intravenous infusion with PACAP-38 can induce migraine attacks. Also, plasma and cerebrospinal fluid PACAP levels are increased during a spontaneous migraine attack, and PACAP antagonists conversely reduced pain sensitivity [18–20]. These investigations suggest that the receptor for PACAP, PAC_1 receptor, may be a target in the treatment of migraine. Mice deficient in PACAP and PAC_1 receptors do not develop hypersensitivity to painful stimuli in neuropathic pain models [19]. PAC_1 receptor monoclonal antibody models are currently being studied for their potential use in migraine treatment.

Non-pharmacologic

Many patients cannot tolerate pharmacologic therapies, do not respond to currently used medications, or simply want non-drug options for treatment of migraine. Also, many migraine patients may be prone to medication overuse headache, and therefore, it is useful to have effective non-pharmacologic treatment strategies.

Non-invasive Neuromodulation

There are several options currently available or in development that utilize neurostimulation at specific anatomical targets to induce neuromodulation of underlying neural circuitry.

Transcranial Magnetic Stimulation

Non-invasive single-pulse transcranial magnetic stimulation (sTMS) delivers a magnetic field from the scalp surface which generates electrical changes in the underlying cerebral cortex. Studies have indicated that the current produced by sTMS can block cortical spreading depression and, when used regularly, may modify dopaminergic transmission and reduce overall nociceptive neuronal hyperexcitability by modulating trigeminothalamic neuronal firing [21].

In a multicenter, randomized, double-blind, parallel-group, sham-controlled study in 2010, Lipton et al. evaluated the efficacy of sTMS and found that it was superior to sham for pain freedom at 2 h (39 vs. 22%, respectively, for a therapeutic gain of 17), with sustained pain-free response rates significantly favoring sTMS at 24- and 48-h post-treatment [22]. In a UK-based survey published 2015 by Bhola et al., 62% of participants reported pain relief, finding sTMS effective at reducing or alleviating migraine pain [23]. There was additional report of relief of associated features including nausea, photophobia, and phonophobia.

A recently published multicenter, prospective, open-label, observational study has suggested that sTMS may be an effective option for the preventive treatment of migraine with or without aura [24]. Included subjects (90% with episodic migraine) underwent preventive daily treatment with four pulses twice daily, along with as-needed acute treatment with three consecutive pulses. Of the 117 patients who completed 3 months of treatment, there was a 2.75 mean reduction of headache days from baseline compared to the performance goal (a statistically derived placebo estimate) of − 0.63 days ($p < 0.0001$). Forty-six percent of participants experienced at least a 50% reduction in headache days, also significantly higher ($p < 0.0001$) than the performance goal (20%).

Supraorbital Transcutaneous Nerve Stimulation

A transcutaneous supraorbital electrostimulation device has been approved by the US FDA for the preventive treatment of migraine. The STS delivers biphasic electrical impulses transcutaneously over the supratrochlear and supraorbital branches of the ophthalmic nerves bilaterally. The device is typically used in daily sessions of 20-min duration. The precise mode of action of supraorbital transcutaneous nerve stimulation remains unclear; however, some have postulated that it may block ascending impulses from trigeminovascular afferents in the pain pathway [25]. Additionally, a study using

FDG-PET in episodic migraine patients found that daily use of the device for 3 months resulted in normalization of previously identified hypometabolism in the orbitofrontal and perigenual anterior cingulate cortical areas in these same patients [26]. Therefore, it has been argued that supraorbital transcutaneous nerve stimulation (STNS) may exert its benefit via neuromodulation of these central areas involved in control of pain and behavior.

In a double-blinded, randomized sham-controlled trial (PREMICE) assessing STNS published in *Neurology* in 2013, researchers were able to provide class III evidence that treatment with a supraorbital cutaneous stimulator is effective and safe as a preventive therapy for migraine [27]. Participants used the device or sham neurostimulation 20 min daily for 3 months. Migraine days per month decreased significantly in the stimulation group (− 29.7%) but not in the sham group (+ 4.9%). Additionally, monthly intake of acute antimigraine medication including triptans was significantly lower in the treated group (− 36.64%) than in the sham group (+ 0.46%). No serious adverse events were reported during the trial, and the device has shown favorable safety and tolerability overall [28].

Non-painful Remote Electrical Stimulation

Remote noxious stimuli have been proposed to yield a generalized analgesic effect via the concept of conditioned pain modulation causing activation of pain inhibitory centers. This has been otherwise referred to as the gate theory of pain control. In a recent model employing this concept, electrodes are placed on the upper arm that generate a stimulus that is high enough to activate the inhibitory pain control system but is subthreshold for actual pain perception.

A recent prospective, double-blinded, randomized, crossover, sham-controlled trial examined the use of skin electrodes applied to the upper arm soon after migraine attack onset for 20 min at various pulse widths. Sixty-four percent of the 71 patients studied experienced more than 50% pain reduction in more than half of their treated attacks, compared to only 26% of those with sham activations ($p = 0.005$) [29]. Relative pain reduction for those using active electrode pulses ranged from 16 to 26%, versus only 2% with sham. Like most migraine abortive therapies, it was found that pain reduction was highest when the device was applied within the first 20 min of attack onset. No significant adverse events were encountered, though 11% of users rated treatment as painful and 28% as unpleasant (compared to 1 and 13% with sham, respectively). In practice, the armband electrical stimulator may be a more desirable approach to non-invasive neuromodulation due to its lower visibility than the other methods described here.

Transcutaneous Vagus Nerve Stimulation

Implanted vagus nerve stimulation has been previously used to treat epilepsy and depression, with incidental benefit noted in some patients with comorbid migraine. Animal models of non-invasive VNS (nVNS) have shown that nVNS significantly alleviates trigeminal allodynia by suppressing the rise in glutamate in the trigeminal nucleus caudalis [30] and inhibits cortical spreading depression by activation of nucleus tractus solitarius, locus ceruleus, and dorsal raphe nuclei (thereby enhancing serotonergic and beta-adrenergic activity) and inhibition of the release of pro-inflammatory cytokines [31].

A non-invasive portable vagus nerve stimulator has been developed that allows for stimulation of the cervical portion of the vagus nerve through the skin on the ventral surface of the neck. Studies utilizing this device in patients with episodic migraine have shown promise. In an open-label, single-arm pilot study published in 2014, 27 patients with episodic migraine were treated with two 90-s doses at the onset of an acute attack. Patients reported pain freedom at 2 h in 22% of the moderate-severe and 38% of the mild attacks [32]. Forty-three percent of patients with moderate-severe attacks reported pain relief at 2-h post-treatment.

The PRESTO Trial, just published in April 2018, recruited 248 patients with episodic migraine with and without aura for a multicenter, double-blind, randomized, sham-controlled trial [33]. Patients self-administered two 120-s stimulations bilaterally within 20 min of attack onset, with repeated stimulations after 15 min if pain had not improved. Those patients who used nVNS had significantly higher pain-free rates at 30 min (12.7 vs. 4.2%, $p = 0.012$) and 60 min (21.0 vs. 10.0%, $p = 0.023$) than sham. nVNS users had significantly higher 50% response rates for no pain than sham (32.4 vs. 18.2%, $p = 0.020$). Adverse effects of nVNS have been infrequent, mostly mild, and transient.

Percutaneous Mastoid Electrical Stimulation

Percutaneous mastoid electrical stimulation (PMES) utilizes stimulation electrodes placed on the mastoid area behind each ear. The exact mechanism of action of PMES remains unclear; however, it has been postulated that PMES can simulate experimental fastigial nucleus stimulation which has been shown to elicit long-lasting suppression of peri-infarction depolarizing waves, a similar process to cortical spreading depression [34]. It has also been hypothesized that PMES may inhibit nociceptive mechanisms involved in migraine pathophysiology, including reduction of neural activity in the trigeminocervical complex.

In a randomized, double-blind, sham-controlled trial published in 2017, investigators saw significant reduction in migraine days with PMES without significant adverse events

[34]. Study participants all carried the diagnosis of episodic migraine with or without aura and received treatment with stimulation electrodes (of different frequencies and currents for PMES vs. sham) placed on the bilateral ear mastoid for 45 min daily for a study period of 3-month duration. The percentage of patients with a ≥ 50% reduction in migraine days in the third month compared with their baseline (50% response rate) was 82.5% in the PMES group (significantly higher than 17.5% in the sham group, $p < 0.001$). Additionally, 60% of patients in the PMES group had a ≥ 75% reduction of migraine days in the third month, and 35% had no migraine attack in the third month. PMES treatment reduced mean migraine days by 58.2% and migraine attacks by 65% (sham − 15.2 and − 14.3%, respectively; $p < 0.001$). These results are certainly promising; however, the authors note that the best treatment mode including current intensity and duration remains unclear.

Caloric Vestibular Stimulation

Caloric vestibular stimulation has long been used as a clinical tool to confirm absence of brainstem function in brain death evaluation as well as in balance disorder diagnostics. Only recently has a device been developed using the principle of caloric vestibular stimulation for potential therapeutic function. Caloric vestibular stimulation (CVS) has potential to provide neuromodulation in areas of the brainstem implicated in migraine pathophysiology.

A multicenter, parallel-arm, block-randomized, double-blinded, placebo-controlled study assessing CVS was undertaken from 2013 to 2016, where 81 subjects self-administered either placebo or active treatments delivered via a headset twice daily for 3 months [35]. Statistically significant reductions in the number of migraine days were observed in the active group as early as the first treatment month, with a final reduction after the total 3-month period of − 3.9 ± 0.6 monthly migraine days ($p < 0.0001$). The active group also exhibited a significantly larger reduction in total monthly headache pain burden than the placebo group. Subjects in both active and placebo groups took fewer migraine abortive prescription medications during the third treatment month compared to their pre-treatment baseline. No serious adverse events were reported with use of the device. Though dizziness or nausea was the most common reason for withdrawing from the trial, these effects were reported in only four active arm subjects (8.1%) and were transient.

Conclusion

Migraine is becoming increasingly recognized as a debilitating neurobiological disease, affecting over 36 million Americans and causing high socioeconomic burden. Within the last two decades, landmark studies have led to significant advancement in our knowledge of the pathophysiology of migraine such that new treatments have been developed to more directly affect specific migraine pathways. We are entering an exciting era of better-targeted and likely better-tolerated medications for both acute and preventive treatment of migraine. Additionally, innovative non-invasive neuromodulation techniques have had very promising results. We anticipate that these emerging, novel approaches will lead to a shift in the significant disability currently caused by migraine.

Compliance with Ethical Standards

Conflict of Interest Kate W. Grimsrud declares no conflict of interest. Rashmi B. Halker Singh has received consulting fees from Amgen and Allergan.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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