Noninvasive neuromodulation in migraine and cluster headache

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Purpose of review
The purpose of this narrative review is to provide an overview of the currently available noninvasive neuromodulation devices for the treatment of migraine and cluster headache.

Recent findings
Over the last decade, several noninvasive devices have undergone development and clinical trials to evaluate efficacy and safety. Based on this body of work, single-pulse transcranial magnetic stimulation, transcutaneous supraorbital neurostimulation, and noninvasive vagal nerve stimulation devices have been cleared by the United States Food and Drug Administration and are available for clinical use for the treatment of primary headache disorders.

Summary
Overall, these novel noninvasive devices appear to be safe, well tolerated, and have demonstrated promising results in clinical trials in both migraine and cluster headache. This narrative review will provide a summary and update of the proposed mechanisms of action, evidence, safety, and future directions of various currently available modalities of noninvasive neuromodulation for the treatment of migraine and cluster headache.

Keywords
cluster headache, migraine, neuromodulation, transcranial magnetic stimulation, transcutaneous supraorbital nerve stimulation, vagal nerve stimulation

INTRODUCTION

Headache is the sixth most common cause of disability in the world [1]. Migraine, due to its high prevalence, accounts for a large proportion of this documented disability [2]. Cluster headache, although less common, is very disabling due to the severity of pain during attacks. Despite the degree of disability, direct and indirect costs, and societal burden of primary headache disorders, many patients are not appropriately treated [3,4]. Multiple factors lead to inappropriate and under treatment of migraine and cluster headache. Poor adherence to treatment regimens is common and multifactorial [5–7]. Acute and preventive medications may be ineffective, have side effects, cause medication overuse headache, and be contraindicated in the setting of medical comorbidities such as cerebrovascular and cardiovascular disease [6,8]. In addition, many medication treatment options are limited in special populations including children, pregnant women, and older adults with medical comorbidities [8]. There is great need for treatment modalities that are effective, are safe with minimal side effects, have no risk of medication overuse headache, and have limited contraindications even in special populations [9,10]. Noninvasive neuromodulation may be a viable treatment option to fill this void.

The concept of neuromodulation in headache started with deep brain stimulation of the hypothalamus for the treatment of cluster headache [11]. Since then it has progressed from very invasive, such as deep brain stimulation [11], to minimally invasive, such as implanted occipital nerve stimulation and sphenopalatine ganglion stimulation [12–14], to the more recent development of noninvasive neuromodulation. Overall, these novel noninvasive devices are safe, well tolerated, and have demonstrated promising results in clinical trials in both

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KEY POINTS

- Several novel noninvasive neuromodulation devices are safe, well tolerated, clinically available treatment options for migraine and cluster headache.
- Single pulse transcranial magnetic stimulation is a safe, well tolerated noninvasive neuromodulation treatment modality with suggested dual utility for acute and preventive treatment for migraine.
- Transcutaneous supraorbital neurostimulation is a safe, well tolerated noninvasive neuromodulation treatment modality with suggested dual utility for acute and preventive treatment for migraine.
- Noninvasive vagal nerve stimulation is a safe, well tolerated noninvasive neuromodulation treatment modality for the acute treatment of episodic cluster headache attacks and migraine.

migraine and cluster headache. In this narrative review, we will review the proposed mechanism of action, evidence, safety, and future directions of various modalities of noninvasive neuromodulation for migraine and cluster headache.

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) utilizes the principle of electromagnetic induction to deliver an electrical current across resistive layers of the scalp, skull, meninges, cerebrospinal fluid, and into the superficial layers of the cortex where it modulates the electrical environment of neurons.

Repetitive transcranial magnetic stimulation in migraine

Initially, it was hypothesized that repetitive TMS (rTMS) could be effective for the prevention of migraine by altering cortical hyperexcitability; however, the clinical data have been inconsistent. Changes to cortical hyperexcitability due to rTMS are highly dependent on stimulation characteristics including frequency, strength, and location of stimulation. This variability is reflected in the clinical studies involving rTMS in the treatment of migraine. A randomized controlled trial (RCT) in chronic migraine using high-frequency tabletop clinic-based rTMS of the primary motor cortex demonstrated a reduction in headache day frequency (−15.6 days) compared with placebo (−8.1 days) [15]. Conversely, low-frequency rTMS was ineffective for the preventive treatment of migraine [16]. Stimulation of the dorsolateral prefrontal cortex has had conflicting results likely due to differing stimulation parameters [17,18]. Overall, the results are encouraging [19▪▪] that once a more consistent treatment protocol has been identified, rTMS may be an effective treatment option for migraine. There are several ongoing studies with rTMS for the prevention of migraine.

Single pulse transcranial magnetic stimulation in migraine

By altering the electrical environment of cortical neurons, single-pulse TMS (sTMS) inhibits cortical spreading depression and alters neuronal excitability [20–22]. In preclinical animal models, sTMS not only inhibits cortical spreading depression, but also the activity of nociceptive thalamic trigeminovascular neurons [23▪▪]. The thalamus may be a potential target for the treatment of migraine as it is a key player in both migraine attacks [24] and the development of central sensitization [25,26]. This data lead to the hypothesis that sTMS may be effective for both acute and preventive treatment of migraine.

Based on this hypothesis and promising pilot studies [27], a multicenter, randomized, double-blind, sham-controlled trial evaluated the efficacy of sTMS using a portable, handheld device for the acute treatment of migraine with aura. In this study, there was a total of 164 subjects, 82 in each group (sTMS-treated versus sham device group), all with migraine with aura. The primary outcome measure was the proportion of subjects who were pain free at 2 h. The sTMS group demonstrated a statistically significant higher proportion of subjects that were pain free at 2 h compared with the sham device group with a clinically significant therapeutic gain of 17% [28]. This study led to the United States Food and Drug Administration (FDA) approval of sTMS for the acute treatment of migraine with aura.

Subsequently, the United Kingdom post market pilot program enrolled a broad range of patients including migraine with and without aura as well as episodic and chronic migraine [29]. In addition, the treatment was tailored to the patient response. In patients with frequent migraine attacks, daily sTMS was recommended. Data collected over 3 months from 190 subjects supported the previously documented acute benefit and suggested a possible preventive benefit in both episodic and chronic migraine [29]. Most recently, a multicenter, prospective, single-arm open label study to evaluate sTMS specifically for the preventive treatment of migraine was completed [30▪]. This open label study used a statistically derived estimate of the potential placebo effect size based on historical controls called a 'performance goal'. The primary endpoint, mean reduction in headache days from baseline compared

with the performance goal, was statistically significant with an effect size of a −2.8 day reduction per month [30▪]. In this study, 46% of the subjects had a greater than 50% reduction in the number of headache days per month which correlated with a reduction in disability and acute medication use [30▪].

TMS has been used safely for decades for diagnosis, monitoring, and treatment of various neurologic and psychiatric disorders without significant short or long-term side effects [31]. Specifically in migraine, sTMS has been well tolerated with no serious device-related adverse events [28,29,30▪]. TMS is contraindicated in patients with epilepsy due to a reported risk of a TMS-associated breakthrough seizures ranging from 0.0 to 2.8% for sTMS and 0.0 to 3.6% for rTMS [32]. In addition, TMS should not be used in patients with metal or conductive materials or implants in the head, neck, or upper body, including cardiac pacemakers, defibrillators, or implanted vagus nerve stimulators due to the risk of lead migration or risk of current induction. The relatively few contraindications to treatment with TMS render it an appealing choice in migraine patients with medical comorbidities including cerebrovascular disease and cardiovascular disease. For these reasons, it is an attractive option for the older adult who has a higher risk of medical comorbidities and polypharmacy. In addition, case reports of the use of rTMS and sTMS during pregnancy have demonstrated that the treatment option was well tolerated by both mothers and newborns without any complications [29,33].

Given the high safety and tolerability of sTMS, this may be an ideal treatment for pediatric migraine. Ongoing studies are exploring the utility of this modality in the pediatric population. In addition, future studies in chronic migraine, medication overuse headache, posttraumatic headache, and other headache disorders are needed.

Overall, sTMS appears to be an effective, safe, well tolerated treatment option for migraine. sTMS has been FDA cleared for the acute and preventive treatment of migraine.

TRANSCUTANEOUS SUPRAORBITAL NEUROSTIMULATION

Supraorbital neurostimulation likely results in the inhibition of nociceptive transmission in small pain-transmitting fibers resulting in modulation of nociceptive activity in the trigeminal ganglion [34]. In addition, supraorbital neurostimulation may also be resulting in central neuromodulation and induction of antinociceptive activity in the anterior cingulate cortex [35▪▪].

Transcutaneous supraorbital neurostimulation in migraine

The transcutaneous supraorbital neurostimulation (tSNS) device noninvasively transmits electrical impulses via an adhesive electrode to stimulate the supraorbital nerves. A randomized double-blind, sham-controlled migraine prevention trial demonstrated a reduction in the mean number of migraine days per month compared with the sham group (6.9–4.8 days in the treatment group versus 6.5–6.2 days in the sham group) [36]. In this study, subjects were instructed to use the device for 20 min of stimulation per day. A small open label 4-month pilot study in 23 chronic migraine patients with and without medication overuse found that only eight of 23 patients had a 50% reduction in monthly migraine days, although over half of the patients had a greater than 50% reduction in acute medication consumption [37]. A small open label trial investigating the device for the acute treatment of migraine found that in 30 patients the mean pain intensity during a migraine attack was reduced by 57% after 1 h and 53% at 2 h [38▪].

This device is typically well tolerated and no serious adverse events have been reported. In one survey study of 2313 device users, 4% of patients reported adverse events, including local pain/intolerance, sleepiness/fatigue, headache, or local skin allergy to the adhesive electrode [39]. Due to high safety of this device, it can be used in the setting of most medical comorbidities, pregnancy, and even in children down to age 8 years according to the website for the device. This device is not recommended for patients with implanted metallic or electronic devices in the head, cardiac pacemakers, or defibrillators. Of note, this has not yet been studied in pediatric migraine for clinical efficacy. Given the safety profile, it is very attractive as a pediatric migraine treatment option; however, studies are needed in this special population. In addition, more rigorous trials in the acute treatment and chronic migraine are needed to support suggested clinical efficacy. Future studies in medication overuse headache, posttraumatic headache, and other headache disorders are needed.

Based on the above studies and safety data, the noninvasive tSNS device has been FDA cleared for the acute and preventive treatment of migraine.

NONINVASIVE VAGAL NERVE STIMULATION

Reports of improvement of comorbid headache disorders with vagal nerve stimulation (VNS) for epilepsy and depression has suggested the possibility of

this neuromodulation treatment modality for migraine and cluster headache [40,41]. VNS may alter the activity of the thalamus, hypothalamus, reticular activating system, amgydalo-hippocampal complex, cerebral cortex, and trigeminal nucleus caudalis via projections to the nucleus tractus solitarius, which receives dural nociceptive afferents [40]. In the preclinical models, VNS has been shown to reduce pain-induced activation of neurons in the trigeminal nucleus caudalis, to reduce pain behavior, and to reduce trigeminal allodynia [42,43,44▪▪].

Noninvasive vagal nerve stimulation in migraine

Noninvasive VNS (nVNS) is performed by a portable device which produces a mild electrical current that is transmitted transcutaneously to the vagus nerve [45]. After promising pilot studies of nVNS treatment in migraine, more rigorous randomized sham-controlled studies have been completed successfully.

The EVENT study was a prospective, multicenter, double-blind, sham-controlled pilot study in chronic migraine prevention with nVNS. The mean reduction in headache days was −1.4 nVNS compared with −0.2 sham [46]. In the open label extension of this study, after 8 months of use, there was a −7.9 mean change from baseline in headache days [46]. More recently, a prospective, double-blind, sham-controlled trial (PRESTO trial) for the acute treatment of episodic migraine attacks found that nVNS was superior to sham for pain freedom at 30 min after use (13% nVNS versus 4% sham) and 60 min after use (21 versus 10%). nVNS was nearly significant at 120 min (30 versus 20%), however, a post-hoc repeated measures test confirmed nVNS superiority over the sham-treated group [47▪▪]. Based on the above data, noninvasive vagus nerve stimulation has been recently FDA cleared for the acute treatment of migraine attacks.

Noninvasive vagal nerve stimulation in cluster headache

An initial pilot study in eight episodic and 11 chronic cluster headache patients who used the device for both prevention (two to three consecutive doses twice a day) and acute attack treatment (three consecutive doses as needed) was encouraging and demonstrated that 79% of patients reported clinical improvement [48]. Subsequently, two large, double-blind, sham-controlled, randomized trials of nVNS for the acute treatment of active episodic and chronic cluster headache attacks were performed [49▪▪,50▪▪]. The primary endpoint was the proportion of patients who achieved pain relief within 15 min without the use of rescue medication [response rate (RR)]. Both studies found that the overall RR was not significantly different from sham. However, subgroup analyses demonstrated that nVNS was effective for acute attack treatment in active episodic cluster headache, nVNS 34% versus sham 11% [49▪▪]; nVNS 48% versus sham 6% [50▪▪]), but not in chronic cluster headache. Based on these two studies, nVNS has been FDA cleared for the acute treatment of episodic cluster headache attacks.

nVNS has been well tolerated and safe in the above clinical trials [47▪▪,49▪▪,50▪▪]. Reports of adverse events have been mild-to-moderate in severity. The most common adverse events included stiff neck, frequent urination, shoulder pain or spasm, lip or facial drooping. Common treatment-related adverse events included neck twitching, raspy voice, and skin redness at the site of stimulation [49▪▪,50▪▪]. Although the vagus nerve does have efferent projections to the heart, no cardiovascular side effects were noted in any of the above studies despite efferent projections of the nuclueus ambiguous to the preganglionic parasympathetic cardiac neurons [51]. It is contraindicated in those with implantable medical devices, such as pacemakers and defibrillators, carotid atherosclerosis, a history of a cervical vagotomy, and clinically significant hypertension, hypotension, bradycardia, or tachycardia. It is not recommended during pregnancy or for children. Future studies in the pediatric population and more rigorous trials in migraine prevention, chronic migraine with and without medication overuse, and cluster headache prevention are needed.

CONCLUSION

In summary, these novel clinically available noninvasive neuromodulation devices provide patients and providers with safe, well tolerated treatment options for migraine and cluster headache. FDA clearance for devices relies on device safety, more so than clinically efficacy. Thus, many of these devices have been FDA cleared and made available for clinical use prior to large, rigorous, RCTs. Future postmarket studies may further define their clinically effective roles. Noninvasive neuromodulation devices appear to have several positive commonalities, including safety and tolerability, minimal contraindications, and potential dual utility for both acute and preventive treatment of primary headache disorders. These are attractive features in patients with medical comorbidities and polypharmacy as well as patients seeking a more simplified or non-oral treatment approach. Overall, noninvasive

neuromodulation for migraine and cluster headache is clinically available, safe, and well tolerated. Future studies in special populations including pediatrics and other headache disorders including chronic migraine, medication overuse headache, and posttraumatic headache are needed to expand their evidence base and clinical role.

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Conflicts of interest

A.S., MD has received consulting fees from Alder, Amgen, Eli Lilly & Company, and eNeura. She is on the medical advisory board for eNeura.

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