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Review Article

Neuromodulation for the Acute and Preventive Therapy of Migraine and Cluster Headache

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Headache disorders are among the most common and disabling medical conditions worldwide. Pharmacologic acute and preventive treatments are often insufficient and poorly tolerated, and the majority of patients are unable to adhere to their migraine treatments due to these issues. With improvements in our understanding of migraine and cluster headache pathophysiology, neuromodulation devices have been developed as safe and effective acute and preventive treatment options. In this review, we focus on neuromodulation devices that have been studied for migraine and cluster headache, with special attention to those that have gained food and drug administration (FDA) clearance. We will also explore how these devices can be used in patients who might have limited pharmacologic options, including the elderly, children, and pregnant women.

Key words: cluster headache, migraine prevention, migraine acute treatment, neuromodulation, neurostimulation

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INTRODUCTION

The idea of using electricity to modulate pain is not new, and dates back as far as the first century. Writings exist that describe how Scribonius Largus, the physician to Emperor Claudius in ancient Rome, would advise his patients with headache to apply a black torpedo fish, a type of electric ray, to their heads hoping that the jolt of electricity that the fish produces would stop their headache pain.[1] Fortunately, our understanding of headache pathophysiology and the role of neuromodulation to help mitigate pain has advanced since that time.

Migraine and other headache disorders are among the most prevalent conditions in the world and are associated with significant morbidity. Migraine specifically affects over 1 billion people and has been identified by the Global Burden of Disease study as the second leading cause of

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disability worldwide, as measured by years lived with disability.[2] Complicating its remarkably high prevalence is the fact that even once appropriately diagnosed, migraine and other headache disorders can be challenging to treat. A recent study revealed that 80% of patients are not continuing their migraine treatment at 1 year,[3] most often due to lack of efficacy or side effects. As there have been devices that have gained FDA clearance for migraine and cluster headache since previous review articles on neuromodulation have been published, our paper will focus on those key studies. We will also briefly review devices in development and also highlight the use of neuromodulation in certain groups who may otherwise have limited treatment options, including the elderly, children, and women who are pregnant.

METHODS

Using the help of a medical librarian, we performed an extensive literature search to identify descriptions of the use and evidence behind neuromodulation for the acute and preventive treatment of migraine, treatment of cluster headache, and treatment in special populations including pregnant women, children, and the elderly patients. We used the terms "cluster headache," "cluster headache/prevention and control," "migraine disorders," "migraine disorders/prevention and control," "acute migraine," "transcutaneous electric nerve stimulation," "neuromodulat*," "implantable neurostimulators," "neurostimulation device," and "neurostim*" to search the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM), and filtered the findings to humans and the English language. Our search returned approximately 200 entries, which we then manually reviewed for articles for this paper. We also hand searched references from these articles.

NEUROMODULATION FOR TREATMENT OF MIGRAINE

Overview.—There is a pressing need to develop new treatments for migraine. From an abortive standpoint, there are several reasons including that existing acute medications might not be effective or tolerated, or are contraindicated due to medical comorbidities. Noninvasive devices make neuromodulation an accessible option to more people, as no surgery is required. While the mechanism of action of these various devices is not always clear, in general, noninvasive neuromodulation devices are placed against the skin, and thought to modulate pain mechanisms by electrical currents or magnetic impulses. Currently, 3 devices have gained FDA clearance for the acute treatment of migraine: single-pulse transcranial magnetic stimulation (sTMS), the supraorbital transcutaneous nerve stimulator (STNS), and the noninvasive vagus nerve stimulator (nVNS).

Several noninvasive neuromodulation devices have been studied for the prevention of migraine, with 2 being FDA cleared for migraine prevention. Most have been evaluated in the prevention of episodic migraine, while some have also been evaluated in the prevention of chronic migraine (Table 1). The exact mechanism of action is not always understood for each device, and many of the studies are small, but results show a reduction of frequency of headache days per month, as well as a reduction of pain severity, pain duration, and use of acute medication. Noninvasive neuromodulation devices may be an option for patients who are struggling with tolerating current therapeutics, who are not achieving full response to current prevention, who prefer a non-medication option, or who need an option that may help them reduce acute migraine medication use. A trial of the device is usually recommended for up to 3 months, as neuromodulation may take longer to see full results. This treatment principle seems especially true for patients with chronic migraine.

Supraorbital Transcutaneous Neurostimulation.—Supraorbital transcutaneous neurostimulation, also known as STNS, is a noninvasive neuromodulation device that has been studied for the prevention of both episodic migraine with and without aura, and chronic migraine as well as the acute treatment of migraine. The exact mechanism of action of STNS in migraine is unclear. Improvement of pain may occur from modulating the peripheral nervous system by stimulation of the supraorbital nerve. This may modulate pain transmission via action on the trigeminovascular system.[4]

Safety and efficacy of STNS was first evaluated on patients with episodic migraine.[5] This study included 67 patients who were given treatment with

Table 1.—Trials of Noninvasive Neuromodulation for the Treatment of Migraine.

Study	Trial Design	Stimulation Dosing	Total Sample Size	Efficacy†	Safety
STNS EM with/without aura[5]	RCT	Once daily treatment for 20 minutes	67	Reduction monthly migraine days: 6.94-4.88 days (P = .023) in treatment No change in sham 50% responder rate: 38.1% (P = .023) in treatment arm	Well tolerated
STNS CM prevention[4]	Open-label Prospective	Once daily treatment for 20 minutes	23	Baseline headache days 20.7 ± 5.7 days/month Baseline acute medication use 20.2 ± 12.4 times/month 8 patients achieved both primary end points 7.6 headache days/month at month 4 6.3 times/month acute medication use at month 4 (no P values provided)	In the treatment group, 3 subjects were unable to tolerate the device due to neck pain (1), worsening headache (1), unable to tolerate paresthesia (1)
STNS Acute migraine therapy ACME trial[5]	RCT	STNS used for 1 hour at the onset of migraine attack	106	Mean change in pain intensity at 1 hour compared to baseline: −3.46 ± 2.32 with STNS vs −1.78 ± 1.89 with sham (P < .0001)	Well tolerated In the treatment group, 4 subjects were unable to tolerate the paresthesia sensation, and 1 developed nausea during treatment
sTMS Migraine prevention ESOUSE study[10]	Open-label Prospective Observational	Four pulses twice daily as prevention and an additional 3 pulses, up to 3 times per attack for the acute treatment of migraine	132	Baseline headache days 9.06 days/month Baseline acute medication use 5.24 days/month 2.75 reduced headache days at month 3 (P < .0001) 50% responder rate: 46% (P < .0001) 2.93 reduced days of acute medication use at month 3	Well tolerated Common adverse events: lightheadedness, tingling, and tinnitus
sTMS Acute treatment of migraine with aura[8]	RCT	Two pulses at aura onset	164	Pain free at 2 hours with sTMS vs sham (P = .0179)	Headache (2%) Migraine (2%) Sinusitis (2%)
nVNS CM prevention[11]	RCT × 2 months, open-label × 6 months	2, 120 second stimulations, 3 times a day for 2 months	RCT = 59 OL = 27	Baseline mean headache frequency 21.5 days per month Primary endpoint met: Safe and tolerable Exploratory endpoints: RCT: 1.4 reduced headache days/month vs −.02 for sham (P = .56) OL: 4 reduced headache days/month	Well tolerated Adverse events reported: upper respiratory tract infections, gastrointestinal symptoms

Table 1.—(Continued)

Study	Trial Design	Stimulation Dosing	Total Sample Size	Efficacy†	Safety
nVNS Acute treatment of migraine PRESTO study[14]	RCT	Bilateral 120-second stimulations to the right and left sides of the neck within 20 minutes of migraine onset; allowed to repeat once after 15 minutes if pain not improved	248	Study failed to meet its primary endpoint of pain free at 120 minutes ($P = .067$), but met several secondary endpoints including pain free at 30 minutes ($P = .012$) and 60 minutes ($P = .023$) and pain relief at 120 minutes ($P = .004$)	Application site discomfort (2.5%) Nasopharyngitis (1.6%)
Auricular t-VNS EM prevention[19]	RCT	Stimulation done up to 4 hours per day over 12 weeks	39	Baseline headache days 19 days per 28 days Baseline acute medication use 9.9 days per 28 days Headache days at study end 1 Hz: −9.6 25 Hz: −5.9 ($P = .035$) Acute medication use at study end 1 Hz: −2.1 ± 4.5 25 Hz: −1.6 ± 4.1 ($P = .96$) 50% responder rates 1 Hz: 29.4% 25 Hz: 13.3% ($P = .18$)	Well tolerated by most Mild adverse events that were self-resolving 18.2% of subjects discontinued the study due to adverse events Adverse events related to problems at the stimulation site, more frequently seen in 25 Hz stimulation group
tDCS EM prevention[23]	Observational pharmacological treatment + stimulation vs pharmacological treatment	Ten procedures of tDCS over 30 days, with each treatment stimulation being given over M1 of the subject's dominant hemisphere for 20 minutes	50	Baseline headache frequency 7 days per month Baseline analgesic use 100% Headache days post study tDCS: 4 days/month post pharmacology: 7 days/month ($P < .05$) Reduction in analgesic use post study tDCS: 72% in migraine without aura, 49% in migraine with aura post pharmacology: 85% ($P < .05$)	Well tolerated Adverse events: tingling under electrodes during stimulation (16.7%), fatigue after stimulation (10%), nausea (3%), headache (3%), and flashes during stimulation (10%)

Table 1.—(Continued)

Study	Trial Design	Stimulation Dosing	Total Sample Size	Efficacy†	Safety
PMES	RCT	Bilateral stimulation daily for 45 minutes	39	Change in headache days PMES: 5.6 ± 2.29 days/month to 2.34 ± 1.79 days per month Sham: 7.85 ± 4.60 days per month to 6.66 ± 4.43 days per month ($P < .001$) 50% responder rate: 82.5% vs 17.5% (sham) ($P < .001$)	Well tolerated
EM prevention[12]					

†Primary endpoint.
Auricular t-VNS = auricular noninvasive vagal nerve stimulation; CM = chronic migraine; EM = episodic migraine; nVNS = noninvasive vagus nerve stimulation; OL = open-label; PMES = percutaneous mastoid electrical stimulation; RCT = randomized controlled trial; sTMS = single-pulse transcranial magnetic stimulation; STNS = supraorbital transcutaneous neurostimulation; tDCS = transcranial direct current stimulation.

STNS vs a sham device. Stimulation was administered daily for 20 minutes for 3 months. Primary outcome measures were change in monthly migraine days and 50% responder rates. STNS was found to be effective in reducing monthly migraine days (6.94-4.88 days, $P = .023$) compared to sham (findings not statistically significant). 50% responder rates for STNS was 38.1% ($P = .023$). Acute medication intake was reduced by 36.7%. STNS was well tolerated with no adverse events.

STNS has also been evaluated for the prevention of chronic migraine in an open-label study.[4] 23 patients were evaluated over 4 months of use of the STNS device. Primary endpoints were 50% reduction in monthly migraine days and 50% reduction in monthly acute medication use. Nineteen patients completed the 4-month trial. Of note, 3 subjects dropped out due to adverse events from STNS, and 1 subject dropped out due to an unrelated medical issue. Baseline headache days were 20.7 ± 5.7 migraine days per month and baseline acute medication use was 20.2 ± 12.4 times per month. Eight subjects achieved both primary endpoints; reduced to 7.6 headache days per month at month 4, and to use of acute medications 6.3 times at month 4 (no P values provided in this study). Six of the 8 responders had acute medication overuse at baseline.

There has been a single randomized, sham-controlled, double-blind study looking at the use of STNS for the acute treatment of migraine.[6] This study, called the ACME trial (acute migraine therapy with external trigeminal neurostimulation) recruited 106 patients from 3 medical centers, all of whom had migraine, and randomized them 1:1 to receive either true or sham stimulation at migraine onset. Subjects were told to treat their attack with their assigned device for 1 hour, and the primary outcome was the mean change in pain intensity (using the 1-10 visual analog scale) at 1 hour compared to baseline. Fifty-two subjects were enrolled in the treatment arm and 54 into the sham device arm, and data from all of these subjects were included in the intention-to-treat analysis. The study met its primary outcome of reduction in pain intensity at 1-hour poststimulation compared to sham (−3.46 ± 2.32 in the treatment group, −1.78 ± 1.89 in the sham group; $P < 0001$. When the findings were

subdivided into migraine subgroups, patients who had migraine without aura also saw a statistically significant benefit with the device compared to sham (−3.3 ± 2.4 in the treatment group, −1.7 ± 1.9 in the sham group; $P = .0006$). In the migraine with aura subgroup, those who were randomized to true stimulation appeared to do better, but these values did not reach statistical significance (−4.3 ± 1.8 for the treatment group, −2.6 ± 1.9 for the sham group; $P = .060$). The device was well tolerated without serious adverse events. With regards to minor adverse events, 2 in the treatment group and 1 in the sham group experienced intolerable paresthesia sensations and were unable to proceed past the nociceptive threshold test phase (experienced by 2 in the treatment group and 1 in the sham group), and 3 subjects randomized to the treatment group stopped the device before the full treatment hour was completed (2 due to painful paresthesia sensations and 1 because of nausea). The FDA has subsequently cleared the STNS device for the acute treatment of migraine.

STNS has a few small studies showing it to be safe in the treatment of episodic and chronic migraine. It is important to note that prevention studies in migraine did not statistically meet the primary endpoints, but STNS is FDA approved for the prevention and acute treatment of migraine. Larger sham-controlled trials are needed to confirm preliminary results. STNS is an option to consider for patients who are seeking non-pharmacologic migraine treatments, and who may benefit from reduction of acute medication use.

Single-Pulse Transcranial Magnetic Stimulation.— Single-pulse transcranial magnetic stimulation, or sTMS, has been studied for the acute treatment of migraine with aura and also the prevention of migraine with and without aura. sTMS is capable of inducing a current to the underlying cortex and changing the firing pattern and excitability of neurons.[7] In migraine, it may disrupt cortical spreading depression, thus modulating the circuits in which pain is induced.[8]

With this premise, sTMS was studied in a randomized, sham-controlled, parallel-group, double-blinded study with 164 patients who met criteria for migraine with aura and experienced aura with at least 30% of attacks.[9] Subjects were randomized 1:1 and instructed to use their assigned device with 2 pulses at the onset of migraine with aura, as soon as possible after the start of the aura and always within 1 hour after aura onset. One hundred two individuals were assigned to the sTMS device and 99 to the sham device. Thirty-seven subjects did not treat an attack and were excluded from data analysis; consequently, 82 subjects from each group (sTMS and sham) were included in the modified intention-to-treat analysis. The primary outcome was pain freedom at 2 hours, and secondary outcomes included sustained pain freedom at 24 and 48 hours. The study met its endpoints, with subjects randomized to the sTMS device being significantly more likely to experience pain freedom at 2 hours (32/82 subjects, 39%) compared to those randomized to the sham device (18/82 subjects, 22%), with a corresponding therapeutic gain of 17% (95% CI 3-31%, $P = .0179$). The sTMS device also did better compared to sham at sustained pain freedom at 24 and 48 hours, and was no different than sham for the typical migraine-associated symptoms of photophobia, phonophobia, and nausea. The device was well tolerated without significant adverse events. In the treatment group, 2 subjects (2%) experienced headache, 2 subjects (2%) experienced migraine, and 2 subjects (2%) experienced sinusitis. These results have led to the FDA clearing the device for the acute treatment of migraine with aura.

The ESPOUSE study was an open-label observational study of sTMS for the prevention of migraine.[10] One hundred and thirty-two patients were in the intent to treat analysis and used sTMS, 4 pulses twice daily as prevention and an additional 3 pulses, up to 3 times per attack for the acute treatment of migraine. At baseline, patients had 9.06 migraine days per month and used acute medications 5.24 days per month. The primary endpoint was reduction in headache days at month 3. The secondary endpoints were 50% responder rates and the reduction of acute medication use. At month 3, subjects had 2.75 fewer days of headache ($P < .0001$). Forty-six percent of subjects achieved a 50% responder rate and used 2.93 fewer days of acute medication ($P < .0001$). sTMS was found to be safe and well tolerated. Most common adverse events with lightheadedness, tingling, and tinnitus, all reported at rates less than 4%.

sTMS is a well-tolerated treatment for migraine. An open-label study suggested it can reduce migraine frequency, and showed efficacy in treating acute attacks. It may reduce acute medication use, which can be helpful in patients who need to use frequent acute medications. Sham-controlled trials are needed to show superior efficacy in migraine prevention and confirm efficacy in acute migraine treatment. As stands, sTMS can be suggested to patients who request non-pharmacological options to treat migraine with the understanding of limited evidence.

Noninvasive Vagal Nerve Stimulation.—Noninvasive vagal nerve stimulation (nVNS) has been studied for the prevention of chronic migraine.[11] nVNS is thought to have an inhibitory effect on brain structures that are involved in production of norepinephrine, serotonin, and involved in central sensitization.[12] In a rat allodynia model, TcVNS was found to have an extended inhibitory effect on the central nervous system by suppressing glutamate increase in the nucleus of the trigeminal nerve.[13] Studies have also shown reduction of cortical spreading depression for up to 2 hours after using nVNS for 4 minutes.[14]

In a double-blind, randomized control pilot trial of the use of nVNS in chronic migraine, subjects were given two 120-second stimulations, 3 times a day for 2 months.[11] Fifty-nine subjects were divided into treatment vs sham stimulation. The baseline mean headache frequency was 21.5 days per month. The double-blind phase was followed by a 6-month open-label study, completed by 27 subjects. The primary endpoint was to assess the feasibility, safety, and tolerability of nVNS. The safety and tolerability of nVNS was found to be similar to sham. Adverse events reported were upper respiratory tract infections and gastrointestinal symptoms. Exploratory endpoints in headache reduction during both the double-blind and open-label phase showed a reduction in headache days for the nVNS treatment group. The study was not statistically powered to assess for significant differences in headache reduction between both groups. During the double-blind phase, the stimulation group had a reduction of 1.4 days less of headache vs the sham stimulation group who experienced 0.2 days less of headache ($P = .56$). Subjects who completed the open-label study were found to have 4 fewer headache days at the conclusion of the trial. Though this trial did not meet its exploratory endpoints of reduced headache days, it was found to be safe and tolerable. nVNS may be considered in patients with refractory chronic migraine, in which other options have failed, or in patients who prefer non-pharmacological treatments. Larger studies are needed to assess if nVNS would provide statistically significant changes in headache frequency over time.

The PRESTO study was a multicenter, randomized, sham-controlled, double-blinded study looking at the nVNS device for the acute treatment of episodic migraine with and without aura.[15] Two hundred and forty-eight subjects were randomized and instructed to use the device within 20 minutes of migraine onset, with the option to repeat treatment after 15 minutes. A single treatment delivery consisted of a bilateral 120-second stimulation applied to the left and right sides of the neck. One hundred and twenty subjects were randomized to true stimulation and 123 were randomized to sham. While the study failed to meet its primary endpoint of pain freedom at 120 minutes (30.4% with nVNS and 19.7% with sham, $P = .067$), it did find that subjects had pain improvement at 120 minutes (40.8% with nVNS and 27.6% with sham, $P = .030$) as well as pain freedom at 30 minutes (12.7% with nVNS and 4.2% with sham, $P = .012$) and 60 minutes (21.0% with nVNS and 10.0% with sham, $P = .023$). The device was safe and well tolerated, with the most common side effects being application site discomfort (2.5%) and nasopharyngitis (1.6%) in those randomized to nVNS. These findings have led to nVNS gaining FDA clearance for the acute treatment of migraine.

EMERGING NONINVASIVE NEUROMODULATION FOR MIGRAINE PREVENTION

Auricular Noninvasive Vagal Nerve Stimulation.—Auricular noninvasive vagal nerve stimulation (auricular t-VNS) has been studied for the treatment of chronic migraine. Auricular t-VNS uses an ear electrode to stimulate thick myelinated sensory fiber afferents in the vagal nerve, which then activates the nucleus of the solitary tract.[16] Use of the device has been shown to reduce pinprick and pressure pain in humans.[17,18]

Auricular t-VNS was studied in a prospective, double-blind, parallel-group trial on adult subjects

with chronic migraine.[19] Twenty-two subjects were treated with 1-Hz stimulation (considered milder stimulation), and 25 subjects were treated with 25-Hz stimulation over 12 weeks for a total of 4 hours per day. The primary endpoint was change in headache days per 28 days. Secondary endpoints were 50% responder rates, change in mean headache intensity on headache days, change in acute headache intake per 28 days, and change in headache disability. Baseline mean headache days for both groups was 19 days per 28 days. Results showed a higher benefit in the 1-Hz group; −9.6 headache days (P = .035) vs −5.9 days for the 25-Hz group. Fifty percent responder rate in the 1-Hz group was 29.4% vs 13.3% in the 25-Hz group (P = .18). There was no difference in headache intensity, acute medication use, or disability measures in either group. Most patients tolerated stimulation, with adverse events reported as mild to moderate and self-resolving. Approximately 18.2% of subjects discontinued the study due to adverse events. Most frequent adverse events were related to problems at the stimulation site, and were observed more frequently in the 25-Hz stimulation group.

Larger sham trials of auricular t-VNS are needed to confirm results, and to see if acute medication use is significantly less in the treatment group. This device is not currently available in the United States.

Transcranial Direct Current Stimulation.— Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation technique that has been studied for the prevention of episodic migraine. tDCS, using a portable, hand-held device, can modulate pain-related neural networks.[20] It has also been shown to cause reduction of analgesic drug intake with pain, and has minimal adverse events.[21,22]

Fifty adult women with migraine with or without aura who were refractory to pharmacological therapy were enrolled to either continue to receive their current pharmacological treatment vs augment current treatment with tDCS.[23] Thirty subjects received 10 procedures of tDCS over 30 days, with each treatment stimulation being given over M1 of the subject's dominant hemisphere for 20 minutes. Efficacy was measured 30 days after the last treatment. Subjects had on average 7 headache days pretreatment, and were reduced by 4 days after treatment (P < .05). There was no change in mean monthly headache days in the non-tDCS group (7-7 days/month). Analgesic use and pain intensity were both reduced in the tDCS-treated arm (100% pretreatment, 72% in migraine without aura, 49% in migraine with aura post-tDCS, no statistics provided), but not in the stable pharmacological arm (85% after study). tDCS was well tolerated, with adverse events including tingling under electrodes during stimulation (16.7%), fatigue after stimulation (10%), nausea, headache (both at 3%), and flashes during stimulation (10%).

tDCS is an interesting neuromodulation concept that needs further investigation in migraine. Large, sham-controlled trials should be considered to confirm findings. tDCS is not commercially available at this time.

Percutaneous Mastoid Electrical Stimulation.— Percutaneous mastoid electrical stimulation (PMES) has been studied for the prevention of episodic migraine. PMES uses electrodes behind each mastoid to induce stimulation of the fastigial nucleus, which can induce suppression of depolarizing waves that are similar to cortical spreading depression.[24]

Juan et al studied PMES as a preventive treatment in episodic migraine with or without aura. The randomized, double-blind, sham-controlled trial evaluated reduction in migraine days per month over 3 months. Bilateral stimulation was performed daily for 45 minutes. The primary endpoint was reduction in the average migraine days over 3 months compared to baseline. Baseline migraine days for the PMES stimulation group were 5.6 ± 2.29 days/month and 7.85 ± 4.60 for the sham stimulation group. The treatment group had a 58.2% reduction in mean migraine days (reduced to 2.34 ± 1.79 days/month) compared to a 15.2% reduction in the sham group reduced to 6.66 ± 4.43 days/month, P < .001). The 50% responder rate in month 3 was 82.5% for the treatment group, and 17.5% in the sham group (P < .001). No significant adverse effects were reported.

PMES for the prevention of episodic migraine has promising preliminary results. As with other devices, larger, sham-controlled studies are needed. PMES is not currently commercially available for use.

Transcutaneous Occipital Nerve Stimulation.—Different frequencies of transcutaneous occipital nerve stimulation (tONS) have been studied for the prevention of episodic migraine without aura. tONS is considered to be effective for migraine prevention in a similar mechanism to STNS.[25]

tONS was studied on subjects with episodic migraine without aura. Three different frequencies of tONS were tested vs sham vs topiramate.[25] Primary outcomes were 50% responder rates, change in headache days, reduction in headache severity, and decrease in headache duration. The frequencies tested were 2, 100, and 2/100 Hz (3-second cycling between both frequencies). Treatment stimulations were given once a day for 30 minutes, and the study was carried out for 1 month. Fifty percent responder rates were as follows in order of stimulation as noted above; 36.36% ($P = .025$), 40.91% ($P < .01$), 36.36% ($P = .025$) vs 4.55% for sham, and 68.18% ($P < .01$) for the topiramate group. Headache day reduction was significant in the 100 Hz (approximately 11-7 days/month, $P = .003$) and topiramate-treated groups (approximately 12-5 days/month, $P < .001$). There was no difference in headache intensity between the arms treated with tONS, but all arms showed reduced headache intensity compared to sham. The 100 Hz tONS group and the topiramate group both showed decrease in headache duration. tONS was well tolerated with all subjects having acanthesthesia, vibrations, or both during stimulation. These sensations were well tolerated.

tONS needs further investigation for the prevention of migraine, but may be a promising option in the future. tONS is not commercially available for use.

Caloric Vestibular Stimulation.—Caloric vestibular stimulation (CVS) has been studied in a parallel-arm, placebo-controlled trial for prevention of episodic migraine with and without aura.[26] Subjects used CVS twice a day for 3 months. The primary endpoint was change in monthly migraine days at month 3. The secondary endpoints were 50% responder rates, change in acute analgesic use, and change in headache intensity. Baseline headache days were 7.7 ± 0.5 days/month for the stimulation group and 6.9 ± 0.7 days/month for the placebo group. The primary and endpoint was met, with subjects having 3.9 days less of migraine ($P < .0001$) compared to 1.1 less days in the placebo group ($P < .048$). Secondary endpoints did not meet statistical significance. The treatment was well tolerated with transient side effects in few subjects (dizziness, nausea, ear discomfort, tinnitus, neck pain). These findings suggest CVS is a well-tolerated treatment. Larger placebo-controlled sham studies are needed to show true benefit. It is not currently commercially available for use.

NEUROMODULATION FOR CLUSTER HEADACHE

Overview.—Though not a rare disease with a 1 in 1000 lifetime prevalence,[27] cluster headache is far less common than migraine and features a relative paucity of available and effective treatments. The 2016 American Headache Society cluster headache treatment guidelines demonstrate only 3 Level A recommendations for acute therapy: sumatriptan subcutaneous, zolmitriptan intranasal, and high-flow oxygen.[28] Patients with cluster headache often have substantial cardiovascular comorbidity and feature a very high rate of cigarette smoking,[29] which may limit or contraindicate the use of triptans and ergotamine compounds as acute treatments for safety reasons. Oxygen is a very safe and effective treatment with fewer contraindications, but in the United States its access is limited secondary to its lack of coverage approval by the Centers for Medicare and Medicaid Services.[30]

For cluster headache prevention, only 1 treatment received a Level A recommendation: occipital nerve injection with steroid, which is conceptualized as a bridge treatment akin to an oral steroid course.[31] Verapamil, the most commonly used preventive therapy,[32] still only has a Level C recommendation despite its widespread use in practice because of the lack of clinical trials in the modern era. This debilitating disease also has a high proportion of patients who have the chronic subform (chronic cluster headache), which is particularly intractable.[27]

Therefore, because of the lack of availability of oxygen and contraindications to the use of triptans with those who have substantial cardiovascular comorbidities, there is a widespread and practical need for new treatments for cluster headache that are

safe, feasible for repeated use, and have few contraindications. For these reasons, neuromodulation is a treatment modality that is appealing to use for cluster headache. Accessibility to autonomic structures intimately involved in pathophysiology includes the vagus nerve and the sphenopalatine ganglion (SPG). This section will focus on randomized controlled trials of neuromodulation devices in the treatment of cluster headache (Table 2). Given the paucity of noninvasive neuromodulation options for cluster headache and the general lack of efficacious treatments for chronic cluster headache in general, this section will also address more invasive forms of neuromodulation.

Vagus Nerve Stimulation.—The neuromodulation treatment featuring the most investigation for cluster headache treatment is noninvasive, external vagus nerve stimulation (nVNS), which is now FDA cleared for both the acute treatment of episodic cluster headache attacks and as adjunctive therapy for cluster headache prevention. The first study that examined this technology for cluster headache was an open-label randomized control trial, using this treatment as preventative therapy as an add-on to current preventative treatment in comparison to patients who were maintained on their usual therapy.[33] The patients in the active treatment arm used the nVNS device and dosed 3 times twice daily on the right side only. The trial featured 97 subjects and patients who were randomized to the nVNS device experienced a reduction of 5.9 attacks per week in comparison to 2.1 attacks per week in the usual care group ($P = .02$). The device was generally well tolerated, with the most common adverse effects being headache at 8%, followed by dizziness, throat pain, and neck pain. No serious adverse effects were observed.

A pair of sham-controlled, double-blinded, randomized controlled trials to treat acute attacks of cluster headache followed this study. The first study was the ACT1 trial, where patients received 3 doses of 2 minutes of right-sided stimulation as needed for an attack.[34] One hundred and thirty-three subjects were treated. The primary end point for the study was having no or mild pain at 15-60 minutes after treatment. About 26.7% of patients in the active treatment group reached this endpoint vs 15.1% in the sham-controlled group ($P = .10$). However, when subjects were stratified according to episodic vs chronic cluster headache diagnosis, statistical significance was reached for those who were treated for acute attacks of episodic cluster headache. The most common adverse event, which occurred in 11% of patients, was lip or facial drooping, pulling, or twitching. There were no serious adverse effects at all in this trial.

The second trial for acute cluster headache attack treatment, the ACT2 trial, featured three 2-minute ipsilateral stimulation episodes of the same nVNS device for an acute attack of cluster headache in a study which included 92 subjects.[35] At 15 minutes, 14% of the overall sample were pain-free vs 12% in the sham group, which was not statistically significant. However, like in ACT1, despite the overall negative result, patients who were treated for episodic cluster headache had a substantial rate of pain freedom at 15 minutes (48% vs 6%, $P < .01$). There were no serious adverse events in this trial.

Sphenopalatine Ganglion Stimulation.—The SPG is an attractive therapeutic target for cluster headache specifically as it represents the key peripheral ganglion involved in cranial parasympathetic outflow, has direct connections to the trigeminal system, and may modulate dural vascular tone.[35] SPG stimulation is a technology requiring surgical implantation of a small device to access the SPG which lies in the pterygopalatine fossa underneath the maxilla.[36] The device is activated by an external, hand-held device to induce an electrical current. Given the invasive nature of the procedure, randomized trials have been limited to assessing its efficacy and safety in chronic cluster headache.

A randomized controlled trial entitled the Pathway CH-1 study was undertaken in Europe for the acute treatment of chronic cluster headache.[37] Thirty-two patients received full implantation surgically of a sphenopalatine ganglion stimulation device, and 28 patients completed the study. After implantation, the patients were randomized to receive full, subperception, or sham stimulation. The patients received titration individually for full stimulation parameters. During the randomized phase of the trial, 67.1% of patients receiving full stimulation had acute pain relief at 15 minutes in comparison to 7.4% of those treated with sham stimulation during their

Table 2.—Randomized Controlled Trials of Neuromodulation for the Treatment of Cluster Headache

Study	Stimulation Dosing	Total Sample Size	Efficacy‡	Safety
PREVA VNS prevention open-label[33]	• 3 × 2 minutes stimulation doses twice daily • maximum of 24 V and 60 mA • Right VNS	97 (all CCH)	• Attacks/week decrease of 5.9 vs 2.1 (P = .02)	• Headache (8%) • Dizziness (6%) • Throat pain (6%) • Neck pain (6%)
ACT1 VNS acute treatment Sham-controlled[34]	• 3 × 2 minutes stimulation • Right VNS	133 (ECH 85, CCH 48)	• No or mild pain 15-60 minutes 26.7% vs 15.1% (P = .10) • Significance for ECH (34.2% vs 10.6%, P = .008) but not CCH (13.6% vs 23.1%, P = .48)	• Lip or facial drooping/pulling/twitching (11%)
ACT2 VNS acute treatment Sham-controlled[35]	• 3 × 2 minutes stimulation • Ipsilateral VNS	92 (ECH 27, CCH 65)	• Pain free at 15 minutes 13.5% vs 11.5% (P = .71) • Significance for ECH (47.5% vs 6.2%, P < .01), but not CCH (4.8% vs 12.9%, P = .13)	• Paresthesias (4%) • Site or skin irritation (4% each)
Pathway CH-1† SPG acute treatment Sham-controlled[37]	• 15 minutes stimulation	32 (all CCH)	• Acute pain relief at 15 min: 67.1% full stimulation vs 7.4% (P < .0001)	• AEs in 15.6% • Three lead revisions • Two devices required explantation • Most with maxillary numbness • 6.3% mild facial paralysis, maxillary sinus puncture
Pathway CH-2† SPG acute treatment Sham-controlled[40]	• 15 minutes stimulation	93 (all CCH)	• Increased pain relief (OR 2.62, P = .008) and freedom (OR 2.32, P = .04) of active treatment relative to sham treatment at 15 min	• Four serious procedure/device related AEs, which resolved
Implanted hypothalamic DBS† Prevention Sham-controlled[46]	• Two 1-month periods • 185 Hz, 60 μs pulse duration • Voltage individually adjusted	11 (all CCH)	• Attacks/week effect difference similar between active and sham stimulation in the on-off group: 0.2 (95% CI −24.0-23.6), and off-on group: −2.7 (95% CI −25.7-20.31); P = .927	• 3 serious AEs: subcutaneous infection, preoperative loss of consciousness with hemiparesis after test stimulation, severe micturition syncope • Nonserious AEs (n = 26) mild, some during open-label extension phase

†Chronic cluster headache only.
‡Primary end point.
AEs = adverse events, CCH = chronic cluster headache, CI = confidence interval), DBS = deep brain stimulation, ECH = episodic cluster headache, OR = odds ratio, SPG = sphenopalatine ganglion, VNS = vagus nerve stimulation.

attacks ($P < .0001$). Adverse events related to the procedure or device occurred in 15.6%, which included 3 lead revisions and 2 devices required explantation. Numbness in the region of the maxillary nerve was experienced in the majority of patients. Mild facial paralysis and maxillary sinus puncture were each experienced in 6.3% of patients.

In this acute treatment study, patients were observed to develop a reduction in cluster headache attack frequency over time. In patients who did not receive treatment with active stimulation (sham), these patients did not receive this benefit until stimulation was initiated in full. Over two-thirds of patients experienced either an acute response from SPG stimulation, a frequency response where attacks diminished by at least 50% in comparison to baseline, or both an acute and preventive response, showing a versatility of the treatment.

The Pathway CH-1 Study was extended in open-label fashion over a period of 2 years where over a third of patients maintained a preventative benefit with at least one complete attack remission period during the study.[38] On average, there was a treatment latency for a preventive effect, with remission period onset averaging 134 ± 86 (range 21-272) days poststimulation initiation. The duration of the longest remission period experienced was 149 ± 97 (range 62-322) days. By the end of the study period, 45% of patients had an acute response to SPG stimulation which in most patients was a consistent response pattern.[39]

A second randomized control trial called the Pathway CH-2 Study was undertaken in the United States with a similar design to the Pathway CH-1 Study that was undertaken in Europe. Preliminary results from this clinical trial were recently made available.[40] This was a larger study, including randomization of 45 patients to SPG stimulation and 48 patients to sham stimulation after surgical implantation. Active treatment was associated with increased pain relief (OR 2.62, $P = .008$) and freedom (OR 2.32, $P = .04$) relative to sham treatment at 15 minutes, with significant greater odds of sustained pain freedom. As in the Pathway CH-1 study, a post hoc analysis demonstrated a preventive benefit over the 28-week study period with a decrease in attack frequency in those randomized to active treatment. The investigators reported 4 serious adverse events related to the procedure or device, which resolved, though full description of these events are pending study publication in a peer-reviewed journal.

Recently, a large open-label, prospective registry study included 97 patients who had an SPG stimulation device implanted with data available for 85 patients who had 12 month follow-up.[41] Over two-thirds (68%) of patients responded in some way to treatment, including 55% who were frequency responders and 32% who were acute responders. Seventy-three percent of patients had postoperative adverse events, most commonly featuring sensory disturbances, postoperative pain, and swelling. Eight patients required lead revision.

Hypothalamic Stimulation.—Given the presumed pathophysiologic role of the hypothalamus related to autonomic dysfunction and periodicity in cluster headache,[42] as well as attack-related hypermetabolism detected in the ipsilateral posterior hypothalamus to the site of attacks,[43] the hypothalamus is a logical neuromodulation target site for patients with chronic cluster headache who have been intractable to other therapies. A randomized control crossover study was undertaken for 11 patients undergoing unilateral posterior hypothalamic stimulation in comparison to sham stimulation.[44] Patients were stimulated with a frequency of 185 Hz and a pulse duration of 60 milliseconds in comparison to sham stimulation. Individual adjustments were permitted to increase the voltage and there were 2 treatment periods (active and sham) that each lasted for 1 month and were separated by a washout period of 1 week. During this randomized control crossover trial, there were no significant differences among the sham and active groups regarding weekly attack frequency. There were no differences in adverse event rates between the active and sham treatment groups, which were frequent but mostly mild. However, 3 serious adverse events occurred, including subcutaneous infection, perioperative loss of consciousness with hemiparesis after test simulation, and severe micturition syncope. At the 1-year open-label phase conclusion, 6 of the 11 patients had at least a 50% decrease in weekly cluster headache attacks, which included 3 patients who were rendered pain-free.

Occipital and Cervical Cord Nerve Stimulation.— Other modalities may potentially be reported in future randomized trials. Implanted occipital nerve stimulation has been studied for cluster headache in nonrandomized studies with the suggestion of efficacy and safety.[45-50] A prospective, multicenter, randomized control trial is underway in Europe to treat cluster headache using this technology.[51,52] A small study of 7 patients with chronic cluster headache also demonstrated efficacy and safety for high cervical cord stimulation but no data from any randomized trials are available.[53]

NEUROMODULATION IN SPECIAL POPULATIONS

Pregnancy.—Women with headache disorders who are pregnant are an underserved population because of a lack of clinical trials for treatment in this particular setting. There are virtually no treatments for headache disorders that lack any potential for teratogenicity. Common acute treatments such as NSAIDs are generally avoided during most of pregnancy, ergotamine compounds are contraindicated, and though the emerging evidence suggests safety for occasional use of triptans,[54] regular and repeated use in pregnant women is of uncertain safety. More established preventative therapies including beta-blockers, tricyclic antidepressants, antiepileptic drugs, and onabotulinumtoxinA all may have the potential for crossing the placenta and teratogenicity of varying degrees.[55] Recently, available treatments for migraine including monoclonal antibodies to calcitonin gene-related peptide (CGRP) or its receptor or small molecule CGRP receptor antagonists are also likely to be avoided in pregnant women given their unknown impact on the developing fetus. In addition, CGRP may be an important peptide in preventing pre-eclampsia,[56-58] for which people with migraine have an elevated relative risk.[59] Therefore, nondrug treatments during pregnancy are ideal in the management of headache disorders.

Existing neuromodulation devices could be potentially safe therapies to use for pregnant women. However, no studies of neuromodulation devices have specifically studied patients who are pregnant. A postmarketing study of single-pulse transcranial magnetic stimulation in the United Kingdom did include 3 pregnant women with frequent episodic or chronic migraine who used the device.[60] All 3 patients treated their attacks repeatedly during pregnancy and reported some degree of benefit, with no labor or delivery complications with healthy children. Vagus nerve stimulation and trigeminal nerve stimulation have been reported in patients with non-headache indications such as depression and epilepsy without any clear signal of teratogenicity attributable to the devices.[61,62] A case was also reported of a woman with chronic cluster headache who effectively used occipital nerve stimulation as a preventive therapy throughout her pregnancy; the device had already been implanted and used preconception.[63] No adverse labor or delivery outcomes occurred.

Though literature reports on using neuromodulation are infrequent, the use of these devices during pregnancy may be preferable to acute and preventive medications with established or unknown teratogenic potential, and if effective could substantially improve maternal well-being. Given the low theoretical risk of these devices in pregnancy, their use in such a context should be discussed by patients seeking non-medication treatment options with their obstetrical clinicians.

Children and Adolescents.—Children and adolescents with migraine are also an underserved population, as most clinical trials including neuromodulatory devices for headache exclude subjects who are younger than 18 years of age. However, a pilot open-label study was undertaken in adolescents for the use of sTMS in teenagers with migraine to assess feasibility for both acute and preventative treatment.[64] In this study, teenagers were treated using sTMS in the same mechanism that was utilized for adults in clinical trials and in practice, with twice daily dosing for prevention and as-needed pulses to be administered as needed for acute attacks.[10] Overall, the device seemed to be feasible and quite safe in this small group of teenage patients. However, the preventative treatment protocol featuring a delay of 15 minutes between 2 series of 2 pulses was challenging on school days, necessitating the safety monitoring board of the study to approve administration of the groups of pulses in rapid succession for prevention without a delay. Once

this change was made, more subjects were able to complete the study. The treatment was well tolerated in this group. A recent, separate systematic review for TMS in children for a variety of indications included aggregate studies of over 4000 children and did not reveal any adverse effects distinct from adults or any clear adverse impact on the developing brain. Recently, FDA clearance for sTMS to treat migraine was expanded to age 12 years and older.

Elderly.—As in pediatric and pregnant patients with headache disorders, patients 65 years of age and older are traditionally excluded from clinical trials for headache disorders, including those of neuromodulation devices. Some postmarketing studies have included some patients older than 65 years, but the data in this specific population is not robust and has not been explored.[65] Elderly patients with headache disorders are particularly in need of safe treatments such as neuromodulation devices because of issues related to higher rates of comorbidities, polypharmacy, drug tolerability, and more frequent medication contraindications.[66] In fact, elderly patients with frequent headache seen in tertiary care have particularly high rates of medication overuse and take drugs on the Beer's list for potentially inappropriate medications in older adults, largely because of the lack of safer and more effective options.[67]

CONCLUSION

The advent of neuromodulation has changed our approach to migraine and cluster headache, and many devices are being used for both acute and preventive treatment. This development has led to treatment versatility of devices functioning as both acute and preventive therapies. These devices are also attractive treatment options for reasons including their lack of contribution to polypharmacy and medication overuse. As they require no surgery, noninvasive neuromodulation devices can be used at any stage of migraine treatment, including as adjunctive or first line options for migraine and cluster headache in patients who might be reluctant to take medications, and should certainly be considered in patients who might have limitations on medication choices. Invasive options should certainly be reserved for those with refractory chronic migraine and drug-resistant chronic cluster headache. Particularly with noninvasive devices, which have gained FDA clearance based on small studies demonstrating safety, ease of use, and potential benefit, we need additional research to confirm the true degree of efficacy versus the role of placebo response in perceived improvement. There are limitations in neuromodulation studies including relatively small sample sizes, challenges with blinding, and ensuring endpoints represent clinically meaningful change.[68] In addition, the use of neuromodulation in routine clinical practice is limited by our lack of understanding of response predictors, as well as cost and access. We anticipate that in the next few years the role of neuromodulation in treating primary headache disorders will be further delineated, and with additional research gain a stronger footing as part of standard of care.

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