

Neuromodulation and Headache

External alteration of nerve activity can be effective in treating headache.

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The International Neuromodulation Society defined therapeutic neuromodulation as “the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.” The stimulus can be electrical, thermal, or magnetic and can result in excitatory or inhibitory changes in the nervous system, depending on parameter settings. Thus, *neuromodulation*, rather than *neurostimulation*, is the preferred term for this new approach in headache management. This brief review describes the US Food and Drug Administration (FDA)–approved noninvasive neuromodulation devices and their characteristics. It also surveys devices in development, as well as a few devices requiring implantation.

FDA-Approved Noninvasive Neuromodulation Devices for Headache Treatment

Single-Pulse Transcranial Magnetic Stimulation

Single-pulse transcranial magnetic stimulation (sTMS; SpringTMS) was initially developed in headache research as a magnetic stimulation device to terminate cortical spreading depolarization or depression (CSD), the basis for migraine aura. Electromagnetic pulses are delivered via a noninvasive device placed on the back of the head. Resulting pulsations travel as far forward as the thalamus and as far down as the neck.¹ These pulses interrupt CSD in laboratory animals.² This finding led to testing of sTMS for acute treatment of migraine-with-aura attacks.

In a randomized sham-controlled trial, 164 patients received 2 pulses of sTMS or sham pulses 30 seconds apart within 1 hour of aura onset.³ The primary endpoint was 2-hour pain freedom, achieved by 39% with verum and 22% treated with sham ($P = .0179$). Sustained pain freedom from 2 to 24 hours was 29% for the sTMS group versus 16% with sham ($P = .0405$). Adverse events were so rare and minimal that the FDA categorized this stimulator as a nonsignificant risk device and approved it for the acute treatment of migraine with aura.

Repeated sTMS pulsing in animals appears to modify cortical excitability, probably by inhibiting or downregulating thalamocortical pain pathways.² Based on these findings, a protocol for daily sTMS delivery was developed to test preventive effectiveness of sTMS in both episodic and chronic migraine.

In 2 studies, after establishing a month of baseline frequency, patients with migraine with 4 to 25 headache days per month were instructed to pulse sTMS 4 times twice daily for 3 months. Neither study was sham-controlled, and the primary endpoint for both was reduction of mean monthly headache days. The study of 132 patients by Starling and colleagues reported about a 3 day per month reduction in the third month of treatment. These studies also noted improvements in $\geq 50\%$ responder rates, decrease in acute migraine medications use, and improvement in scores on the Headache Impact Test.^{4,5}

During the preventive trials, patients were allowed to pulse extra times during the day on an as-needed basis and reported efficacy in acute treatment of migraine attacks with and without aura. As a result of these studies, the FDA approved sTMS for both acute and preventive treatment of migraine in July 2017, and the device is now commercially available by prescription. The current availability requires patients to rent the device with a monthly fee using a preloaded sim card that provides stimulation for a prespecified number of months. The FDA approval implies indication for use in the acute treatment of migraine with and without aura and in the preventive treatment of both episodic and chronic migraine, as patients with each of these subtypes were included in the studies.

Transcutaneous Supraorbital Neurostimulation

Transcutaneous supraorbital neurostimulation (tSNS; Cefaly; also called external trigeminal stimulation (eTNS)) provides electrical stimulation of both supraorbital and supratrochlear nerves to modulate downward central pathways involved in the genesis of migraine. The modulation access is via these afferent branches of the first division of the trigeminal nerve (ophthalmic) (V1).

tSNS was studied in 2 randomized controlled studies: 1 for preventive and 1 for acute treatment of migraine. In the

preventive trial, 67 patients with episodic migraine placed the device on the forehead and stimulated for 20 minutes daily for 3 months; half received sham stimulation. There were 2 primary outcomes: reduction of migraine days in the third month, which was not significant, and the responder rate of $\geq 50\%$ reduction in migraine days/month, which was achieved by 38.2% with active and 12.2% with sham stimulation ($P = .023$).

Adherence in this study was a problem. Patients were supposed to stimulate for 20 minutes daily for 90 days, for 90 sessions. In the verum group, they stimulated for an average of only 55 days, and in the sham group, they stimulated for an average of only 49 out of the 90 days.⁶

The acute trial was presented at the International Headache Society in Vancouver in September 2017 in a late-breaking abstract by Chou et al.⁷ In this trial, 57 patients with either episodic or chronic migraine, experiencing a migraine attack for at least 3 hours with stable pain intensity for at least 1 hour, were administered tSNS stimulation or sham for 1 hour. The primary endpoint of the trial was the mean change in visual analog scale (VAS) pain score at 1 hour, which was reported as statistically significant in active treatment versus placebo. Interestingly, although patients in the study reported improvement in their pain, there was no reduction in the amount of acute rescue medication taken within 24 hours after the tSNS stimulation.

Based on these 2 studies, the FDA approved tSNS as a non-significant risk device for both preventive and acute treatment of migraine in September 2017, and the dual device is commercially available with a prescription. Patients currently buy the device and electrodes online with a provider prescription, and electrode replacements are generally required every 3 months of use thereafter.

Noninvasive Vagal Nerve Stimulation

Noninvasive vagal nerve stimulation (nVNS; gammaCore) was tested in randomized controlled trials for the preventive and acute treatment of both cluster headache (CH) and migraine. This device preferentially electrically activates vagal afferent pathways, not those vagal efferents that cause bradycardia and bronchoconstriction. Stimulation of the device inhibits rat CSD, central trigeminovascular/cervical, and thalamocortical pathways, suggesting that many of the neuromodulation devices work at final common pathways.⁸

The randomized controlled trial of nVNS in the prevention of chronic CH (CCH) was not sham-controlled but compared addition of nVNS to standard of care CCH prophylaxis. The study demonstrated decreased attacks per week from baseline, $\geq 50\%$ responder rate, and decreased use of rescue medications and oxygen versus standard of care.⁹

For acute treatment of CH, 2 randomized controlled trials compared nVNS with sham stimulation for relief at 15 minutes. Both studies instructed patients with CH to use 3 cycles of 2 minutes as the primary neuromodulation. In patients with epi-

sodic CH (ECH), both studies showed effectiveness in terminating attacks. However, nVNS was not found to be effective for acute treatment of CCH attacks.^{10,11}

For chronic migraine prevention, a randomized sham-controlled study of nVNS found the device failed to statistically significantly reduce migraine days at 2 months, but suggested decreased days over the next 4 months, so it may take longer than 2 months for this neuromodulation to be effective.¹²

For acute episodic migraine treatment, the randomized sham-controlled trial of nVNS failed to show statistically significant 2-hour pain freedom compared to sham, but demonstrated benefit at 30 and 60 minutes for 2-hour headache relief, and for the $\geq 50\%$ responder rate.¹³

The FDA approved nVNS as a non-significant risk device for the acute treatment of ECH in April 2017, with the recommended use of 3 cycles of 2-minutes each at attack onset. In January 2018, the FDA approved nVNS for acute treatment of migraine with a recommended protocol of 2 cycles of 2 minutes each and the option of 2 more 2-minute cycles 15 minutes later if pain has not yet resolved. The device is commercially available with a prescription; patients buy a certain number of stimulations on a renewable sim card.

Noninvasive Neuromodulation Devices Currently in Development for Headache Treatment

Caloric Vestibular Stimulation

The vestibular nerve enters the brainstem at the cerebellopontine angle at the same level as the trigeminal afferents, and crosstalk between vestibular input and trigeminal input suggests a potential mechanism for migrainous vertigo and the possibility of modulating the trigeminocervical system by inhibiting vestibular involvement. A noninvasive caloric vestibular stimulator (Scion) used a novel approach of heating and cooling the vestibular nerve in quick and limited excursions and was successful in preventing episodic migraine in a randomized sham-controlled study. The trial of 46 patients utilized a home use protocol in which the subjects wore the device for 20 minutes twice daily. The study was positive for the primary endpoint of reduced migraine days per month in the third month. The number of headache days per month was reduced by ~ 3 headache days per month. The study was also positive for secondary endpoints of responder rate and decreased use of acute medications.¹⁴ No significant adverse events were reported, and the device is designated a non-significant risk device for migraine prevention.

Remote Nonpainful Electrical Upper Arm Skin Stimulation

Remote nonpainful electrical upper arm skin stimulation (Nerivio Migra) with a non-significant risk device was studied in a randomized controlled trial of 71 patients for the acute treatment of episodic migraine. The proposed mechanism of

action for this approach is that the device activates descending inhibition pathways via a conditioned pain modulation effect, an endogenous serotonergic brainstem pain mechanism based on the premise that pain inhibits pain. Once there is a noxious stimulus at any body location (eg, migraine), it may be inhibited by a second stimulus at a different location (eg, the device) presented at high intensity, and that stimulus is not perceived as painful.

This was a prospective, double-blinded, randomized, crossover, sham-controlled trial in which migraineurs applied electrodes to the upper arm soon after attack onset for 20 minutes, at various pulse widths, for up to 20 attacks. There was 50% pain reduction for 64% of subjects, based on the best of 3 pulse width stimuli, versus 26% in the sham group over 299 treatments.¹⁵

Combined Occipital and Supraorbital Transcutaneous Nerve Stimulation

Combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS, Relivion) was studied for acute treatment of episodic migraine in a randomized controlled trial by Hering-Hanit, reported at the International Headache Society meeting in 2017.¹⁵ This device may create inhibitory synergy by electrical neuromodulation from both trigeminal and cervical afferents.

In the study, 30 patients acutely treated one migraine attack, initiated at no more than 90 minutes after the attack onset, with treatment for 45 minutes. There was a significant reduction of the average pain VAS score in the treatment group versus an increase in the pain VAS score in the control group (−79.2% vs +14.9%, respectively; $P = .0002$). Pain-free response rates significantly favored the active OS-TNS device at 2 hours ($P = .0031$) and at 24 hours ($P < .05$) post treatment. Superiority of the OS-TNS device was also shown for functional disability ($P = .0004$) and photophobia ($P = .002$). No device-related serious adverse events were recorded¹⁶, so this device is likely to be categorized as another nonsignificant risk noninvasive device.

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) has been studied in various areas of application for prevention of migraine, including to the prefrontal, motor, sensory, supraorbital, and visual cortex.¹⁷⁻¹⁹ These devices deliver inhibitory current in single or multiple repeated sessions, sometimes given seasonally, to achieve migraine reduction. Ongoing studies will be necessary to optimize the correct montages and the best presentation frequency and duration of treatment.

Invasive Neuromodulation in Development Sphenopalatine Ganglion Stimulation

Sphenopalatine ganglion stimulation (SPGs) is being studied for acute and preventive treatment of both CH and migraine. CH pathophysiology suggests a central generator in the ipsilat-

eral posterior hypothalamus that sends efferent fibers, which synapse in the superior salivatory nucleus. Preganglionic parasympathetic fibers exit the superior salivatory nucleus and synapse in the SPG. Postganglionic parasympathetic nerves from the SPG target the end organs, manifesting in both pain and cranial autonomic signs and symptoms in CH.

A minimally invasive transoral approach was developed for delivering a wireless SPG neurostimulator (Pulsante), which is screwed in place ipsilateral to the side of the CH attacks. Activation of SPGs at low frequency precipitates cluster attacks, while high-frequency stimulation terminates the attacks, confirming that low frequency is excitatory while high frequency inhibits the outflow from the SPG in CH.²⁰

In a randomized, sham-controlled trial of this implanted SPG stimulator for acute treatment of CCH attacks, 15-minute pain relief was reported in 67.1% of actively treated attacks and in 7.4% of sham-treated CCH attacks ($P < .0001$). The device also caused a reduction in frequency of attacks, a preventive effect, and 61% of patients had either acute relief in $\geq 50\%$ of attacks and/or a $\geq 50\%$ reduction in attack frequency.²¹ The durability of these effects for the SPGs was reported across 2 years.²² Adverse events with implanting the SPGs appear for the most part to be mild and transient and consistent with side effects described in other oral surgeries.²³

As a result of these studies, the SPG is approved and commercially available in the European Union for use in patients with CH. A regulatory trial for CCH is underway in the United States at the time of this writing (January 2018). Migraine and other trigeminal autonomic cephalalgias are potential targets for SPGs as well.

Occipital Nerve Stimulation

Occipital nerve stimulation (ONS) with a surgically implanted stimulator, a tunneled wire, and implanted programmable generator with battery has been studied for prevention of chronic migraine. Again, using neuromodulation, the occipital nerve would theoretically provide an afferent conduit to down-regulate central pain pathways.

Three different studies of ONS for prevention of chronic migraine using 3 different systems were all either negative or equivocal. None reached the primary endpoint, and all had methodologic problems.²⁴⁻²⁶ In unfavorable comparison with noninvasive neuromodulation, adverse events with implanted ONS are an important problem and include electrode migration, intolerance to paresthesias, cable breakage and discomfort, muscular spasm, infection, and battery depletion. In 2014, the European Union rescinded approval of the St Jude Genesis ONS device for treatment of headaches due to these issues.

Deep Brain Stimulation

Deep brain stimulation (DBS) has been used to prevent intractable CCH. An electrode is implanted in the CH cen-

tral hypothalamic generator. Magis and Schoenen²⁷ summarized 14 case series from 2005 to 2013 with 65 patients implanted in the ipsilateral posterior hypothalamus for CCH, with a mean of 2.8 years follow-up. These reports were all case series, as there are no randomized controlled trials. Improvement was seen in 66% of the implanted patients with CCH, with a mean of 42 days required with the stimulator on to achieve effectiveness. Turning off the stimulator blind to patients resulted in clusters recurring. The clusters then stopped again when the DBS was turned back on, strongly suggesting efficacy.

Adverse events are a substantial and potentially mortal problem with DBS for CCH. These complications include oculomotor disturbance, vertigo, infection, sleep disorders, and intracerebral hemorrhage in 2/64 cases (1 fatal), a rate of 3%. Transient ischemic attacks and stroke have also been described. DBS has been abandoned for the most part in treating patients with CCH, given noninvasive and minimally invasive alternatives.

Conclusions

Many devices providing noninvasive neuromodulation for preventive and acute treatment of primary headache disorders have reasonable evidence for effectiveness and non-significant risks with use. The FDA has approved tSNS and sTMS for both preventive and acute treatment of migraine. Noninvasive vagal nerve stimulation is FDA approved for acute treatment of ECH attacks.

New developing neuromodulation devices show promise through small randomized controlled trials that suggest therapeutic benefit. These evolving and emerging treatments include caloric vestibular stimulation, remote nonpainful electrical upper arm skin stimulation, OS-TNS, and cathodal tDCS. Minimally invasive transorally implanted SPG stimulation shows promise for both acute and preventive treatment of patients with CH. More invasive neuromodulation devices providing ONS and DBS are limited by substantial adverse events. ■

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