Non-Invasive Neuromodulation: The Next Step in Migraine Care?

Neuromodulation devices represent a unique opportunity to patients for effective treatment of migraine in a cost-effective fashion with no significant side effects.

By Stewart J. Tepper, MD

Headache medicine is in the midst of a significant shift. As we await the arrival of monoclonal antibodies for the treatment of migraine, a less heralded but arguably equally important innovation in this field is non-invasive neuromodulation. The basic concept of neuromodulation is to inhibit central pathways to prevent and/or terminate primary headache disorders. Currently, three non-invasive neuromodulation devices are approved for use, while others are making their way through regulatory channels and may eventually expand the market as well as the demand.

Despite representing a bold new path in the headache/migraine spectrum, neuromodulation has arrived on the scene rather quietly. Access to neuromodulation devices has been restricted for a variety of reasons. Nevertheless, both general neurologists and headache specialists should pay close attention to neuromodulation technology, as it may offer the potential for a paradigm shift in headache medicine.

Non-invasive Neuromodulation: FDA-approved Devices

Transcutaneous Supraorbital Neurostimulation. The first non-invasive neuromodulation device that obtained FDA approval is a transcutaneous supraorbital neurostimulator (tSNS), also known as Cefaly. The company recently released an updated version known as the Cefaly II. The device sits on a set of electrode pads on the forehead over the procerus and activates bilateral supraorbital nerves. It modulates inhibitory input via the supraorbital nerves, enters the trigeminocervical complex, and modulates headache/migraine downward preventively.

The FDA approved the device based on results from a randomized controlled trial published in the journal Neurology. The trial had two primary endpoints: the number of migraine days at the end of the third month of stimulation, and the 50 percent responder rate. The device was to be worn for 20 minutes a day. Of note, the trial evaluated episodic migraine patients and therefore did not encompass chronic migraine or medication overuse headache.

The study failed on the first primary endpoint but was positive for the second endpoint, which was statistically significant. As noted, the instructions to study participants were to wear the device for 20 minutes a day for three months, after which researchers observed a significant reduction in the responder rate for number of headache days. However, compliance rates were fairly poor. A number of patients did not continue to wear the devices for 20 minutes a day, which made the interpretation of the data more difficult.

The device has both a high-intensity and a lower-intensity setting, so patients that can’t tolerate the higher setting can move it to the lower setting. In Europe and Canada, the device is approved with three different settings: a preventive setting, an acute setting, and a relaxation setting. At the time of this writing (May 2017), a randomized controlled trial for the tSNS device in acute treatment of migraine is underway.
The total initial cost of the device is roughly $400. Patients who aren’t able to tolerate it can return it within 60 days for their money back. However, it is worth pointing out that the stimulation didn’t show benefit until the third month. Therefore, I often tell patients who are able to tolerate treatment to continue for at least 90 days, even if they aren’t seeing effect earlier.

Tolerability is variable. Some patients find it difficult to use even on the lower setting, whereas others are not bothered. Currently, no commercial or government payers are reimbursing for the device, so it is up to individual patients to pay if they want to try it.

Single-Pulse Transcranial Magnetic Stimulation. The second FDA approved device is a single-pulse transcranial magnetic stimulator (sTMS) called SpringTMS (eNeura). SpringTMS delivers single magnetic pulses to the back of the head, likely to the occipital cortex. The pulse of the magnet does not extend much more than halfway toward the front of the skull. Therefore, the magnetic pulse likely does not go much further anterior than the thalamus.

This device probably has at least two mechanisms of action. It was developed initially to interfere with what is referred to traditionally as cortical spreading depression, but what is increasingly being referred to as cortical spreading depolarization. Cortical spreading depression (CSD) is a slow activation of cortical neurons that represents the basis for migraine aura. As occipital neurons in a visual aura fire slowly across the occipital cortex, these neurons are depolarized, and the patient sees the effect of the neurons within their occipital cortex firing.

During a visual aura, the ocular dominance columns of Hubel and Weisel are activated. Some of these code for circles or half circles, or zigzags, or movement, and so the activation of these columns sequentially causes the positive, slowly moving visual aura that people see in migraine. In laboratory animals, sTMS has been shown to very clearly terminate CSD by Peter Goadsby and colleagues. The initial idea behind sTMS was to use it at the beginning of a migraine with aura and terminate the aura and the migraine that follows.

A randomized control trial evaluated two pulses of this device taken at the beginning of the aura in patients with migraine with aura. The primary endpoint was pain freedom in two hours. Roughly 40 percent of patients with the active device were pain-free at two hours, and about 20 percent of the sham-stimulated patients were pain-free at two hours. Based on these results, the FDA approved sTMS for acute treatment of the pain of migraine with aura, with two pulses to be delivered at the beginning of migraine with aura.

Subsequently, the device was tested in open-label studies with a preventive paradigm. The preventive paradigm was four pulses in the morning and four pulses at night, with additional sets of pulses on an as-needed basis if the patient either got an aura or the patient felt a migraine accelerating. One of these studies has been published, and one has been presented partially at several meetings. Both studies included patients with from four to 25 headache days per month, meaning that the trials included patients with episodic migraine as well as chronic migraine. The primary outcome measure was a decrease in headache days at the end of three months with steady use of four pulses twice daily. Both studies found very prominent drops in headache frequency at the end of the three months of daily use.

In the UK, use of the device is for both acute and preventive treatment of migraine, both episodic and chronic. In the US, the manufacturer may seek regulatory opinion on a preventive indication based on the two open label studies.

Currently sTMS is only available to rent. The patient can rent the device for three months at a time initially, which costs about $150 per month. After that, the amount per month is variable, depending on how long they’re signing up for. sTMS is likely to cost between $200 and $250 per month to rent over a year.

In the roughly 150 patients I have seen use the device, those who are compliant usually seem to benefit from it. Also, acute treatment outcomes appear stronger for those who have used it longer and preventively. As extra pulses replace medications, use of triptans and acute medicines then goes down. We’ve even tried it not just for chronic migraine and episodic migraine, but also for some more difficult to treat primary daily persistent headache disorders such as new daily persistent headache. Some patients with new daily persistent headache reported benefit and signed up for a full year because nothing else has worked.

It is worth exploring the questions of why this device works preventively and why it works preventively in patients that don’t have aura. A hypothesis is that sTMS modulates thalamocortical pathways that are part of the migraine integration, and presumably modulates them...
downward slowly. Animal models as well as human models have shown thalamocortical effects from the sTMS.

**Non-invasive Vagal Nerve Stimulation.** A third non-invasive neuromodulation device was approved by the FDA in April 2017. Called gammaCore (Electrocore), the device is a non-invasive vagal nerve stimulator (nVNS) that’s placed on the neck over the vagus nerve and then stimulated for 90 seconds to two minutes. This stimulation is then repeated in the acute treatment approach for cluster or migraine headache. The two cycles are repeated three times a day in the preventive protocol.

Already approved in Europe and Canada, nVNS has been studied extensively in randomized controlled trials in more therapeutic areas than any of the other non-invasive devices.

Two randomized controlled studies evaluated nVNS for acute treatment of cluster headache, the ACT-1 and the ACT-2 studies. The ACT-1 study has been published in *Headache*, and the ACT-2 study has been described at meetings. The two studies showed identical findings. Acute use the non-invasive vagal nerve stimulator could terminate episodic cluster headache attacks, but did not very effectively or statistically significantly terminate chronic cluster headache attacks. Based on these studies, the FDA approved the device for acute treatment of episodic cluster headache attacks.

The device has also been tested in the prevention of cluster headache. In that study, nVNS was either added to standard of care medications or not, and the addition of the use of the device daily reduced cluster attack frequency as a well as use of acute medications.

nVNS was tested in a randomized controlled trial for chronic migraine. The device did not reach significance for reduction of headache days at two months, but showed promise in reducing headache days at longer time points in the open label extension.

nVNS also appears to both terminate CSD and down-regulate thalamo-cortical pathways, suggesting that inhibitory non-invasive neuromodulation may enter the CNS from different points but converge in mechanisms of action similarly.

**On the Horizon**

**Caloric Vestibular Stimulation.** A caloric vestibular stimulator (CVS, Scion Neurostim) has been tested in the prevention of migraine. The vestibular nerve comes into the brainstem at the same level as the trigeminal nerve. There is likely crosstalk between the vestibular system and the trigeminal system, for example, in migrainous vertigo, and it appears possible to neuromodulate the trigeminal central system by stimulating the vestibular nerve in an inhibitory manner.

The device is worn in a pair of headphones with a small cone stimulator in the ear. CVS very quickly heats and cools the vestibular nerve with very tight limits on how high, low, and quickly the temperature changes, so that the vestibular nerve cannot adapt to these quick changes in temperature. By limiting the excursions of heat and cold, the engineers prevent the thermal stimulus from triggering all of the bad results typical of caloric stimulation, ice water calorics, and hot water calorics, that cause patients to be profoundly vertiginous and nauseated and vomit, in addition to triggering nystagmus and oscillopsia.

In a randomized controlled trial that has been presented at several meetings, patients with episodic migraine wore the device for roughly 20 minutes twice daily. CVS reduced the number of migraine days, also hit the 50 percent responder rate outcome measure, and reduced medication use. In addition, the study also looked at cognition and other features of migraine, all of which improved. Adverse events were basically indistinguishable from the sham device. A second randomized controlled trial is underway in the US at the time of this writing.

**Non-painful remote electrical stimulation.** In March 2017, a non-painful remote electrical stimulator was described in a randomized controlled trial. This is a device wrapped around the upper arm, and three pulse widths were tested acutely and compared with placebo, with the best setting resulting in a 50 percent reduction in migraine pain in almost two thirds of patients. Further studies are clearly indicated.

**Invasive Neuromodulation Sphenopalatine Ganglion Stimulation.** Other neuromodulation devices under investigation and/or are approved in Europe include a minimally invasive sphenopalatine ganglion stimulator device (Pulsante, ATI), a very small device that is placed into the pterygopalatine fossa through the mouth. It is being tested in the US for acute treatment of chronic cluster headache attacks. A previous published randomized controlled trial showed a preventive effect and/or an acute effect in chronic cluster. This device has potential

**ARTICLE AT A GLANCE**

Non-invasive neuromodulation represents a promising new avenue to treat headache. While the three devices currently available are cost-effective in comparison to other modalities and have been found effective and well tolerated, none is reimbursed by third-party payers.

32 PRACTICAL NEUROLOGY MAY 2017
for acute and preventive treatment in both cluster and in migraine, but is not approved for use in the US at the time of this writing.

**Occipital Nerve Stimulation.** Implanted occipital nerve stimulators (ONS) have been studied in three randomized control trials for prevention of chronic migraine. The studies of ONS in prevention of migraine did not reach significance, and ONS is associated with many side effects, including pain, lead breakage, lead migration, depletion of the battery, and infection. Because of these adverse events, the European Union in 2014 rescinded approval of the previously approved ONS for headache. There is a randomized controlled trial on ONS for prevention of cluster headache underway in Europe at the time of this writing.

### Shifting the Paradigm

The time may be fast approaching when patients will have four or more non-invasive neuromodulation devices to choose from, with varying side effects profiles, conveniences, and cost, for acute and/or preventive treatment of primary headache disorders. However, despite the availability of multiple non-invasive neuromodulation devices, their wider use has been limited by the fact that they are not currently covered by third-party payers. The patient with commercial insurance with chronic migraine must usually fail two to three categories of anti-migraine prevention, anti-depressants, anti-epilepsy drugs, and anti-hypertensives, before being approved for onabotulinumtoxinA, although this is the only FDA approved treatment for chronic migraine. Only then will insurers reimburse for onabotulinumtoxinA treatments. However, onabotulinumtoxinA treatment, including drug, provider fee, room fee, pharmacy storage fees, etc., may in some centers cost between $10,000 and $20,000 per year. This raises the question: “Why don’t the third-party payers require patients to try and fail at least one of the FDA-approved non-invasive preventive migraine devices before moving on to botulinum toxin?” The non-invasive neuromodulation devices are all considerably less expensive to access than a year of onabotulinumtoxinA.

Another point to consider is that many patients prefer not to take daily drugs for headache and migraine prevention. Side effects and tolerability concerns are significant in most oral medications commonly used for migraine and cluster prevention. So, hypothetically, if nVNS is effective in one out of every three patients in the termination of episodic cluster headache attacks, it might still make sense to try that device before injectable sumatriptan or oxygen, in many cases.

Neuromodulation devices represent a step between conventional oral preventive therapies and biologics, such as onabotulinumtoxinA and eventually, monoclonal antibodies. Non-invasive neuromodulation constitutes a realm that will likely continue to grow. If sTMS gets approved for prevention of migraine and tSNS gets approved for acute treatment of migraine, patients would have two devices that work both ways, for both prevention and acute migraine treatment. SPG stimulation and nVNS have both already demonstrated acute and preventive effects for cluster headache and are both tested for migraine. Thus, neuromodulation technologies offer a significant potential for a paradigm shift in headache treatment, albeit a shift that requires a combination of either patient demand or payer realization of that potential. It is very important to increase the visibility and awareness of these evolving modalities, to optimize headache care with what the FDA terms “minimal risk devices.”

Non-invasive neuromodulation represents a tremendous opportunity for neurologists and patients alike to change the way headache care is approached. Few would deny that the prospect of treating primary headache disorders without drugs or with decreased use of drugs is exciting. While the modality is still early, with three FDA approved devices, all with limited indications, we will likely see more approvals and expanded indications in the near future.

As the realm of neuromodulation continues to grow, providers will have many questions to consider, not only about the role of these devices in care, but also how their availability may impact use of other therapies. For example, assuming that payers eventually come on board to pay for neuromodulation, should providers first try non-invasive devices before even writing a prescription for a drug? This is just one of many questions to be addressed if the market and demand for neuromodulation devices continues to expand. If the efficacy of these devices is corroborated and adverse events remain as negligible as so far they appear to be, their impact could be massive. It behooves headache providers to pay close attention to this developing frontier.

**Stewart J. Tepper, MD** is Professor of Neurology at the Geisel School of Medicine at Dartmouth College, where he is also Director of the Dartmouth Headache Center.