Noninvasive Neuromodulation of Migraine: A Comprehensive Guide for Patients and Clinicians

A path to healing and taking control …

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A path to healing and taking control …

This guide is for both you as the patient, staring with a brief overview, and for your prescriber to understand in greater detail (See Deep Dive into the Evidence) what your options are, and how to select and obtain a device (See Comparison Tables).

If you're considering any of these devices, consult with your healthcare provider to determine which option might be best for your migraine management needs and to help you with obtaining the appropriate device.

For You, the Patient - An Overview

Introduction

Living with migraine can be an all encompassing task, taking time away from our lives and our work. We know, migraine is more than just the headaches. Migraine can cause a range of symptoms affecting your quality of life even when there is no headache. This is why migraine is a leading cause of disability worldwide. The "traditional" treatments to treat and prevent migraines rely heavily on medications of which all medications carry risks and potential adverse affects. And, treatments for woman of child bearing years, teens and kids are greatly limited where medications are often not an option.

There are newer options available that don't involve taking drugs. These are called noninvasive neuromodulation devices, and they have been shown to be both safe and effective through various studies. Several noninvasive neuromodulation devices have received approval from both the U.S. Food and Drug Administration (FDA) and European regulatory bodies, meaning they meet strict safety and efficacy standards. Overall, they are portable and can be used safely when you need to treat or prevent migraine.

> A significant advantage of the noninvasive devices is they can help you feel more in control and improve your quality of life by potentially breaking the cycle of migraine and migraine symptoms.

These devices cannot cause medication overuse headaches, which can occur when people rely too heavily on pain relief drugs. They are potentially particularly beneficial for women who are pregnant, breastfeeding, or planning to become pregnant, as there are no medication risks and there is proven safety and efficacy in one of the devices highlighted below. Similarly, for teenagers and younger children who have even fewer options, these devices are a valuable alternative and some are specifically approved to be used with teens and kids.

The brain processes involved in migraines are complex. These devices work by targeting specific pathways in the brain that are involved in migraines. By focusing on these pathways, neuromodulation devices can help stop migraine pain and prevent future attacks. Currently, there are several devices available, each targeting treating and preventing migraine slightly differently.

Understanding Migraine Treatment Devices Options

There are four devices approved for use in treating migraines that work by delivering electrical stimulation through the skin to affect the nervous system. These devices offer different approaches to managing migraines by using electrical stimulation to target specific nerves involved in migraine attacks. Here's a brief overview of each:

Stimulation delivered through the skin to affect your brain:

GammaCore™ (nVNS)

- **How It Works**: This hand held device uses gentle electrical stimulation on the neck to target the vagus nerve. It can be used both to stop a migraine in progress and to help prevent future attacks.
- **Who Can Use It**: gammaCore™ can be used by adults who suffer from migraines with and without aura.
- **Why It Helps**: Stimulating the vagus nerve can interrupt the pathways in the brain that contribute to migraines, providing relief and reducing the frequency and severity of attacks.

Cefaly™ (eTNS)

- **How It Works**: Cefaly™ is worn on the forehead and stimulates the trigeminal nerve, that is involved in migraines. The device delivers a mild electrical impulse to this area.
- **Who Can Use It**: Designed for adults, Cefaly™ can be used to treat migraines with or without aura and is suitable for both acute treatment and prevention. This is the only device discussed here that does not need a prescription,
- **Why It Helps**: By targeting the trigeminal nerve, Cefaly™ can help modulate the pathways that lead to migraine pain, offering relief and preventing future episodes.

Relivion™ (eC-TONS)

- **How It Works**: Relivion™ is the newest of these devices worn as a head-band. The head-band targets both the trigeminal and occipital nerves, providing a comprehensive approach by delivering electrical stimulation to both these areas.
- **Who Can Use It**: This device is intended for adults who have migraine with or without aura. It is currently only approved for treating acute migraine - aborting - not for prevention. Approval for prevention is pending.
- **Why It Helps**: By addressing multiple nerve pathways involved in migraines, Relivion™ can help stop or reduce the severity of migraine attacks

Nerivio™ (REN)

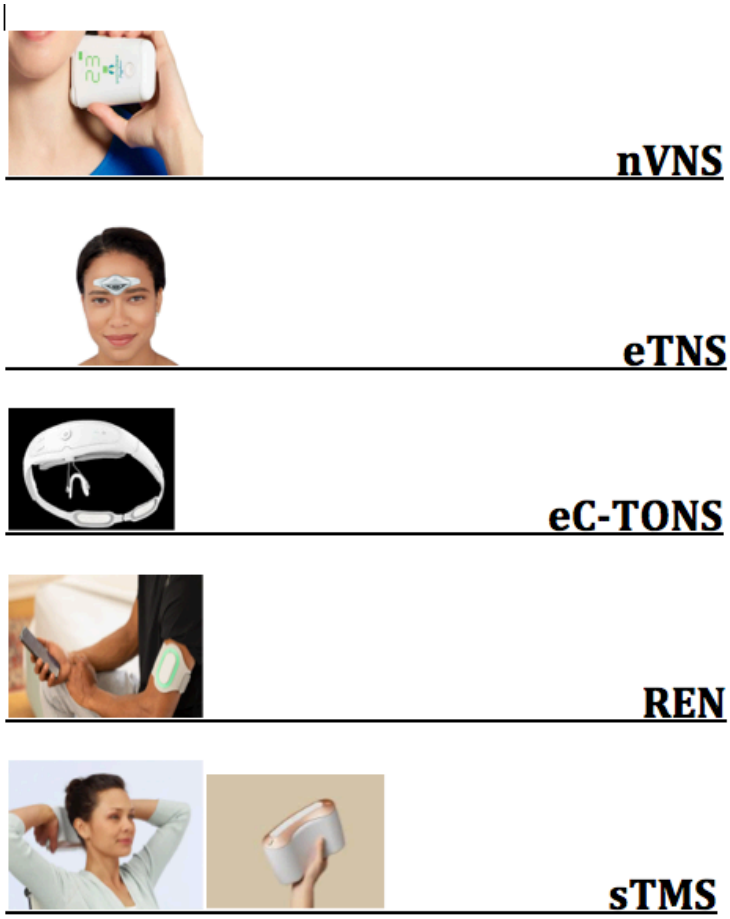
- **How It Works**: Nerivio™ is a wearable arm band that uses a gentle electrical stimulation to help manage migraine pain as well as the accompanying symptoms of acute migraine through a process called "conditioned pain modulation."
- **Who Can Use It**: Suitable for adults, adolescents and kids eight years and older, Nerivio™ is used for both acute treatment of migraines and prevention.
- **Why It Helps**: Nerivio™ can help reduce pain by promoting the body's natural pain inhibition processes, offering relief during a migraine attack and reducing frequency of attacks.

Stimulation to your Brain:

SAVI Dual™ by eNeura (sTMS) is a portable, hand-held device approved for treating migraines. It is different from the above devices as it uses a method called single pulse transcranial magnetic stimulation (sTMS) to help manage migraines.

- **How It Works**: The device delivers a very brief magnetic pulse (feels like a tap on the back of the head) directly to the brain. This technique disrupts a brain process called cortical spreading depression (CSD), that is linked to migraine attacks and symptoms.
- **Who Can Use It**: The SAVI Dual™ is approved for use by adults and adolescents aged 12 and older. It can be used both to stop a migraine once it starts and to prevent migraines from occurring, whether they come with aura (visual or sensory disturbances) or not.
- **Why It Helps**: Research has shown that CSD plays a role in both types of migraines—those with aura and those without. CSD increases the sensitive and excitability of the brain that can lead to migraines. By targeting this sensitivity and excitability, the SAVI Dual™ helps to manage and reduce migraine symptoms and prevent future attacks.

Device Images*



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Noninvasive Neuromodulatoin of Migraine Clinician Guide:

Deep Dive into the Evidence
and
Device Selection for Patients

Introduction

Noninvasive neuromodulation interventions for aborting and preventing migraine continue to emerge as significantly important alternatives to pharmaceutical treatments. There are several devices with demonstrated safety and efficacy through clinical trials that meet U.S. Food and Drug Administration (FDA) clearance and European Union's Medical Device requirements (Conformité Européenne - CE marked). The potential superiority of noninvasive neuromodulation comes to light when we consider the key demographic affected by migraine women of child bearing years[1] whose mainstay for treating headaches when either pregnant, lactating, or planning for pregnancy, are medically limited with a heavy emphasis on non-pharmaceutical prevention.[2, 3] The current best-evidence prescription options pose notable risks such as triptan's cardiovascular effects (for any patient with cardiovascular risks);[4] and calcitonin gene-related peptide (CGRP) medications of which are contraindicated in women who are pregnant, lactating, or planning for pregnancy.[5] Similar limitations apply to pediatric and adolescent patients. In the US, only four types of migraine-specific drugs are approved for abortive treatment of migraine in patients aged 12–17 years (rizatriptan, almotriptan, sumatriptan–naproxen, zolmitriptan) and only topiramate is FDA-approved for preventing migraine in adolescents 12 years of age and above.[6] Most migraine pharmaceutical prophylaxis for adolescents is off-label with heavy emphasis on cognitive behavioral therapy and trigger avoidance.[7] The majority of randomized controlled trials of the efficacy of preventive medications for pediatric patients have failed to demonstrate superiority to placebo leaving only behavioral interventions with trigger avoidance[7] and for aborting migraine only over the counter medications. For all patients, the safety profiles of noninvasive neuromodulation devices eclipse those of pharmaceutical treatments (as discussed below), match in efficacy[8, 9], and offer cost-effectiveness with reduced healthcare utilization.[10, 11, 12, 13] Moreover, there is zero risk of medication overuse headache from these devices.

Migraine's effects are not limited to the ictal headache affecting the nervous system.[14] It is a syndrome marked by dread of the next migraine and burdensome interictal symptoms (See Figure 1. "Migraine Cycle")[15] including for some a symptomatic prodrome up to 72 hrs prior. The migraine syndrome even for those who may only experience the ictal migraine headache once a month results in loss of control and decreased quality of life, explanatory of why migraine is the second leading cause in adults of years lived with disability in the world.[1] The current commercially available personal-use neuromodulation devices can provide not only a sense of control but potentially a path to breaking the syndromic cycle of migraine, thus, improving quality of life.

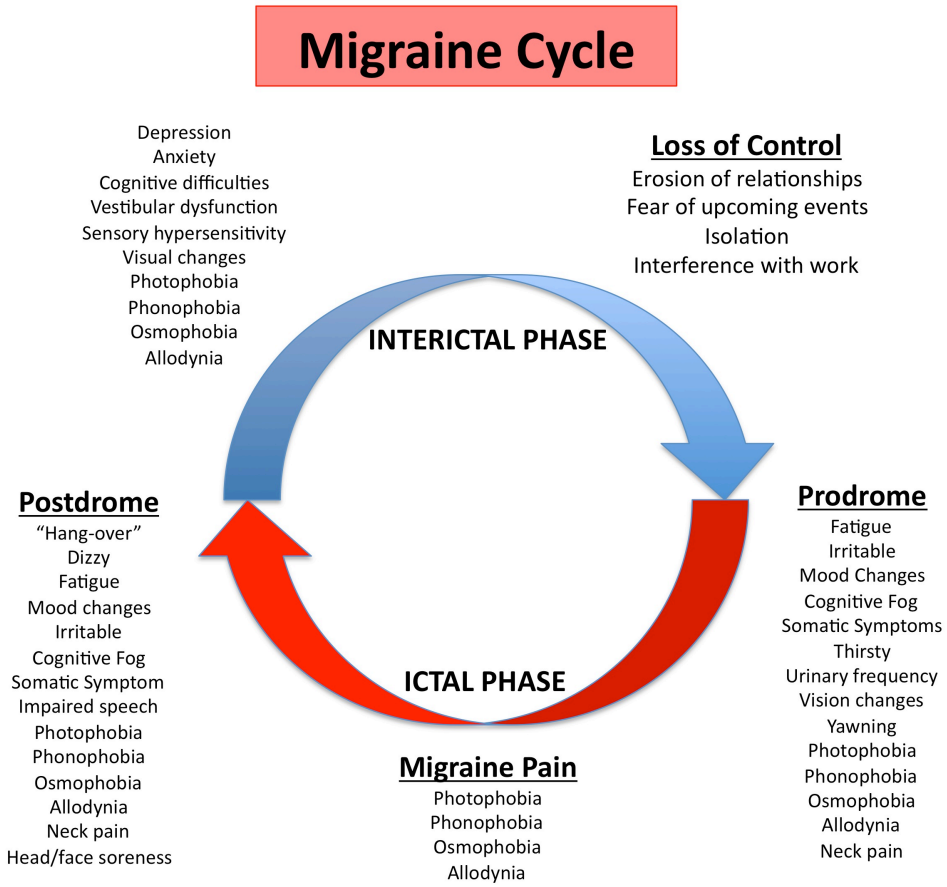

Figure 1.

Noninvasive neuromodulation devices are designed to target specific neural pathways involved in migraine pathophysiology. The pathophysiology of migraine involves several interrelated mechanisms, the most prominent of which are the trigeminovascular system and cortical spreading depression or depolarization (CSD). Key contributing peripheral afferents include trigeminal, occipital, and cervical pathways of the trigeminovascular system (Figure 2, "Migraine Pathways")[15] that converge at the trigeminal cervical complex (TCC) and share subcortical and cortical pathways. Peripheral activation of these pathways with subcortical and cortical interplay ultimately leads to antidromic release of CGRP [16], a principal neuropeptide implicated in the neurovascular and neuroinflammatory symptoms of migraine[17], including migraine pain and increased sensitization to migraine.[18,19] CSD is a slowly propagating wave (2–6 mm/min) of neuronal and glial depolarization that spreads across the cortex from occipital to frontal regions followed by a prolonged inhibition (15–30 mins) of cortical activity that can precede an acute migraine attack.[20] It was initially believed that CSD was only associated with the aura symptoms experienced by 1/3 of migraine patients 20-40 mins before migraine pain.[20, 21] However, evidence from animal and human studies has shown that CSD can be associated with migraine both with and without aura, as well as the photosensitivity symptoms of the ictal and interictal phases of migraine.[18, 22, 23, 24] CSD and CSD predisposition lowers the threshold for triggering the trigeminovascular system[25] and hence release of CGRP and onset of migraine pain.[18, 26, 27] In addition, neuroinflammatory cortical glutamate is also released from peripheral activation of trigeminovascular system and CSD, increasing neuroinflammation and central sensitization to recurrent migraine.[17, 18, 28, 29]

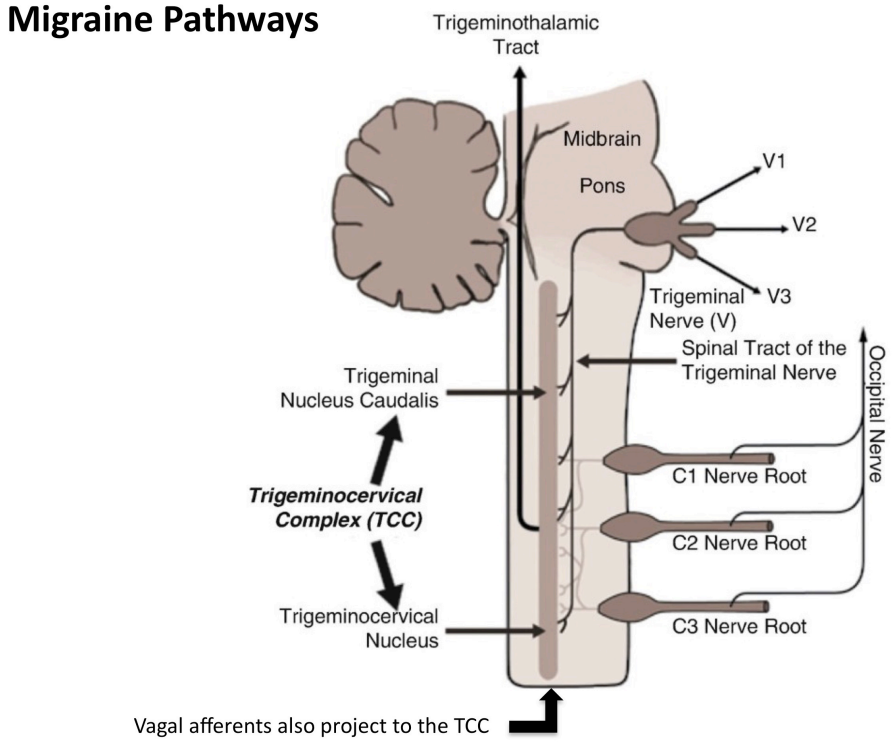

Figure 2.

The limited neurovascular theory of migraine centered around the trigeminovascular system that lead to the development of triptans decades ago (and is still a core intervention) has evolved to one which now recognizes migraine as a heterogeneous and complex brain disorder involving both neurons and astrocytes where the susceptibility and perpetuation of the migraine syndrome is due to recurrent activation of peripheral and central pathways that then synergistically increase susceptibility. [2, 18, 19] Neuromodulation targeting key peripheral afferents in this paradigm (trigeminal, occipital, and cervical) and CSD has been shown clinically to both abort migraine pain and prevent migraine, hence, theoretically interrupting the cycle of central sensitization.

As our understanding of migraine pathophysiology evolves - such as genetic as well as brain cortical and subcortical structural and functional predispositions to migraine - neuromodulation will likely play an increasingly important role in comprehensive management strategies, and perhaps move to first-line treatment preventing the cycle of migraine pain from happening in the first instance. Currently, the two main categories of clinically available noninvasive neuromodulation devices fall under transcutaneously delivered electrical stimulation (four devices) and cortical stimulation (one device). This chapter explores the current FDA-approved/CE marked neuromodulation devices for migraine treatment - gammaCore, Cefaly, Relivion, Nerivio and SAVI Dual (eNeura) - with a synopsis of keystone clinical trial data and germane supporting evidence. Comparing devices can be challenging as they act on different proposed migraine pathways and have unique treatment protocols. The International Headache Society's (IHS) guidelines and recommended criteria for clinical trial design for treating migraine are the "gold standard" for weighing safety and efficacy research and are included throughout this discussion.[30] It is important to note that the IHS guidelines

specifically for neuromodulation were not published until 2021.[31] Prior IHS guidelines were focused on pharmaceutical trials but still serve as a measure for the preceding neuromodulation investigations and were used in most studies in some manner as discussed below. Finally, guidance on how to select a device for patients is briefly outlined.

Transcutaneously Delivered Electrical Stimulation Devices
See images of devices and table comparisons at end of guide.

There are currently four FDA cleared[32] and CE marked transcutaneously delivered electrical stimulation[33] devices that act on the peripheral nervous system to centrally modulate migraine:

- Cervical non-invasive vagal nerve stimulation (nVNS): gammaCore™
- External trigeminal (V1) nerve stimulation (eTNS): Cefaly™
- Combined Trigeminal (V1) + Occipital nerve stimulation (eC-TONS): Relivion™
- Remote Electronic Neuromodulation (REN): Nervio™

The first three devices (nVNS, eTNS, and eC-TONS) target migraine afferent pathways (vagal, trigeminal, and trigeminal+occipital, respectively) feeding into the trigeminovascular system and the TCC theoretically modulating subcortical and cortical centers to abort or prevent migraine (expanded below). The fourth device, REN, does not directly act on the known migraine pathways; it is thought to act through transcutaneous Aδ and C-fiber stimulation resulting in top-down central pain inhibition through conditioned pain modulation (CPM)[34] of migraine.[35, 36]

Cervical non-invasive vagal nerve stimulation (nVNS): gammaCore™

Based on clinical evidence of safety and efficacy, the FDA granted clearance in 2018 for the portable handheld nVNS device, gammaCore™, for aborting episodic migraines in adults with and without aura. It had been cleared in 2017 for episodic cluster headache treatment. Using vagal nerve stimulation for managing headaches emerged from anecdotal narratives of migraine relief in individuals receiving implanted devices for epilepsy leading to the innovative exploration of nVNS for migraine relief.[37, 38] Since this spark, nVNS has accumulated robust clinical trial data on its safety and efficacy, and animal and human data regarding its mechanism of action. The nVNS device in the US is now approved with six indications for headache: aborting and preventing episodic and chronic migraine (ages 12 years or older)[39]; aborting and preventing cluster headaches; and treatment of hemicrania (continua and paroxysmal). In Europe it is CE marked for the same primary headaches in adults as well as medication overuse headache and trigeminal autonomic cephalalgias.

How the device is used:

For abortive migraine treatment, patients are directed to use the device as soon as they feel the onset of migraine pain. It is held at the side of the neck over the vagal nerve; a treatment lasts two mins (timed by the device). Two treatments are used in succession, ideally on both sides of the neck. The device can be used repeatedly if pain does not abate; it is recommended that patients wait 15-20 mins between the first two treatments and then 2 hrs based on clinical trial data.[40] For prevention, the device is used three times a day (TID) where each session is two, two-mins treatments. The level of intensity is controlled by the patient where the device delivers a peak Voltage of 24-V and max 60 mA using a proprietary 5 Mhz sine wave burst

repeated every 40 ms (25 Hz). The device can be used with all oral medications for migraine, nerve blocks, or chemo-denervation.[41] It allows for a maximum of 30 treatments in a 24-hour period. All patients have a contact at gammaCore to guide set-up and use, troubling shooting; online tutorials are available. The device has its own charging stand and depending on use a charge can last for several days allowing for portability. It can fit in a pocket and requires a contact gel. Gammacore is available only by prescription.[42]

Key Clinical Evidence:

It was the PRESTO trial[43] that led to initial FDA clearance of this device for episodic migraine with and without aura in adults. This trial used the gold standard of migraine clinical design, the International Headache Society's (IHS) criteria established for pharmaceutical studies. The clinical trial IHS guidelines for neuromodulation[44] research was not formulated until 2021 (after PRESTO) and took the lead from the investigators of PRESTO[45] for creating the neuromodulation guidelines. The industry sponsored PRESTO trial was a multi-center (all in Italy), prospective, double-blind, sham-controlled, randomized trial with three (4 four-week) phases following IHS recommend criteria for measuring consistency overall (a "run-in" phase to assure participants were stable on all medications notably migraine preventatives; the double blind treatment period; and an open-label period the consistency phase). The PRESTO study is one of the largest trials (N=243) examining neuromodulation with 234 participants going on to the open label period providing Class I evidence following IHS clinical trial criteria.

The active device used the same stimulation parameters as the FDA approved device. The sham device delivered a low-frequency (0.1 Hz) biphasic-signal transcutaneous current. The treatment protocol for initiating treatment was the same as for the prescription device: at onset of migraine pain a two min treatment to each side of the neck (four mins total) and to be completed within 20 mins after the onset of pain. Participants could re-treat at 15 mins if pain was not resolved and re-treat at 2 hrs if not resolved. Use of abortive medications before or at 2 hrs was considered a treatment failure. An intention to treat (ITT) analysis was used (gammaCore, n = 120 vs sham, n = 123) and the IHS recommended primary endpoint of being pain-free for the first treated migraine attack without rescue medication use at 120 mins. For the first treated attack, key secondary and exploratory outcomes included pain-freedom at 30 and 60 min; pain-relief (as defined by IHS guidelines) at 30, 60, and 120 min; mean percentage change in pain score from baseline to 30, 60, and 120 min; and treatment efficacy of associated symptoms (i.e., nausea, vomiting, photophobia, and phonophobia) at 120 mins. Consistency of response during the open-label period followed IHS guidelines: ≥50% responder rates at 120 mins for both pain freedom and relief in participants with at least 2 treated migraine attacks.

For the primary end point of pain-freedom at 120 mins, gammaCore was better than sham in reaching this endpoint, but it was not statistically significant (gammaCore, 30.4% vs sham, 19.7%; p = .067). It was later shown that the sham was an active control,[46] possibly explaining the loss of significance at 120 mins under this analysis. Also, a secondary repeat-measures analysis[47] across 30, 60, and 120-mins did demonstrate superiority of gammaCore over sham for the pain-free outcome at 120 mins with an odds ratio of 2.3 (95% CI, 1.2-4.4, p = .012).[43] In fact, for the secondary outcome measures for the first treated migraine attack, the pain-free rate was higher in gammaCore than in sham participants at 30 mins (gammaCore, 12.7% vs sham, 4.2%; p = .012) and 60 mins (gammaCore, 21.0% vs sham, 10.0%; p = .023). For secondary symptoms, there was no difference. (Few participants in both groups were experiencing associated symptoms at the time of initial treatment.) The responder results for nVNS were overall consistent during the open-label period and the proportion of participants who responded at 120 mins for ≥50% of their attacks was significantly higher with nVNS than with the sham device for both pain-freedom (p = 0.020) and pain-relief (p = 0.026). Participants did not know which device they were using, found nVNS treatment

acceptable and feasible, and any adverse events were mild and transient (skin discomfort, nasopharyngitis, or other headache) with no severe adverse events.

Additional Evidence and Supporting Studies[48]:

In a separately published paper of the PRESTO data[49] regarding pre-defined secondary end points, the nVNS group vs sham had significantly greater decreases in pain score from baseline for the first migraine attack and all attacks at 60 mins (First *P*= .029; All p = 0.029) and for the first attack at 120 mins (First p =0.011). These results were also consistent in the open label phase. Another post-hoc analysis of the PRESTO study[50] found the proportion of participants who did not require rescue medications was statistically significantly higher in the nVNS group versus sham for the first attack (nVNS, 59.3%; sham, 41.9%; p=0.013) and all attacks (nVNS, 52.3%; sham, 37.3%; p=0.008). After the first attack, there was a statistically significant, clinically relevant greater reduction in pain intensity scores in the nVNS group by at least one point (on a 4 point scale) at 30 mins (nVNS, 32.2%; sham, 18.5%; p=0.020), 60 mins (nVNS, 38.8%; sham, 24.0%; p=0.017), and 120 mins (nVNS, 46.8%; sham, 26.2%; p=0.002). When pain intensity was initially mild, the proportion of participants with no pain was higher in the nVNS group than sham at 60 mins (all attacks: nVNS, 37.0%; sham, 21.2%; p=0.025) and 120 mins (first attack: nVNS, 50.0%; sham, 25.0%; p=0.018; all attacks: nVNS, 46.7%; sham, 30.1%; p=0.037). This is important as patients reliant on pharmaceutical abortive interventions tend to wait to treat when pain is severe to avoid limitations in availability of medications. (Notably, in the US dispensing of triptans is limited to eight pills a month in most cases to avoid medication overuse headaches and adverse events). It would be advantageous for patients to have a readily available alternative with a low side-affect profile to treat *before* symptoms became severe.

Regarding migraine prevention, there are three industry-sponsored studies, a small pilot RCT (EVENT) and two larger RCTs (PREMIUM and PREMIUM II). The EVENT study[51] preceded the PRESTO study and evaluated the safety, tolerability, and efficacy of nVNS prevention in adults with chronic migraine with and without aura resulting in Class II evidence. The larger PREMIUM[52] and PREMIUM II[53] trials also investigated the safety and efficacy of nVNS for the prevention of migraine in adults with and without aura, but the first PREMIUM study focused on episodic migraine, while PREMIUM II examined both episodic and chronic migraine. Though the PREMIUM studies did not achieve significance with the primary outcomes, there still were clinically meaningful, statistically significant results (discussed below) and both of these studies demonstrated that consistency and duration of treatment was crucial to a positive clinical response.[54]

The EVENT study was a prospective, multi-center, double-blind, randomized, sham-controlled design (ITT population n=30 for nVNS and n=29 for sham) conducted at six tertiary care headache centers in the US. There were three phases meeting IHS design criteria: a one-month baseline phase to collect pretreatment data, followed by a two-month randomized, sham-controlled phase, and then a six-month open-label phase during which all participants (n=27) received nVNS treatment and data for the open label was collected for per protocol (PP) analyses. The migraine prevention protocol was two, two-min stimulations like the current clinical protocol. However, unlike the current clinical protocol of bilateral stimulation, the study treatment was limited to only the right side of the neck.[55] The sham device had no electrical current. The primary endpoints were safety and tolerability. The efficacy endpoints were the change in number of headache days per 28 days and acute medication usage under an ITT analysis. Post-hoc efficacy analyses examined percent treatment responses defined as ≥50% reduction from baseline in the number of headache days. Safety analyses were performed on all 59 participants from the ITT population. The device was safe and tolerable where, again, adverse events were mild and transient. At month 2 there was no statistical difference in headache days, but 10.0% of participants (3/30) from the nVNS group had a ≥50% response, and 3.3% (1/30) experienced a ≥75% response. *No controls experienced a ≥50% response at any time of the study*. Of the 27 participants who went on to complete the open label phase,16 were initially randomized

to nVNS. For the sixteen nVNS participants who continued to the open label phase, the mean change from baseline in headache days after 8 months of treatment was significant −3.6 (95% CI −6.3 to −0.87; p = 0.02) and the proportion of nVNS participants who achieved a ≥50% response. Hence, persistent nVNS use was associated with reduction in the number of headaches. days and increase in the ≥50% reduction response directly supporting accrual of clinical benefit with longer treatment periods.

The PREMIUM[56] and PREMIUM II[57] trials were also multi-center, randomized, double-blind, sham-controlled investigations with a run-in period, treatment period, and open label period. The study prevention protocols were the same in both PREMIUM studies as the current clinical paradigm, two consecutive treatments for two mins (four mins total) over the vagus nerve in the neck *bilaterally* three times a day - not just the right side of the neck as in the EVENT study. For the PREMIUM study, the sham device did deliver a low frequency current but not for PREMIUM II. For both studies, participants had to be stable on all medications entering the study and could not change or start new medications. Notably, migraine preventative medications were not permitted until the open label period.

For the first PREMIUM trial the primary efficacy outcome was the mean reduction in number of migraine days from the run-in period (baseline) to the last 4 weeks of the 12-week double-blind period. Secondary outcomes were headache day reduction and acute medication days, as well as ≥50% responder rates for migraine, headache, and acute medication days. The ITT population was 332 patients total (nVNS, n=165; sham, n=167) and 299 participants entered the open label phase with 187 completing the study (nVNS, n=100; sham, n=87). Not all participants adhered to the TID treatment protocol, but most 83.6% (138/165) in the nVNS group and 83.8% (40/167) in the sham group demonstrated adherence of at least 67% per month. There was no significant difference in the ITT analysis but post hoc analysis of patients with≥67% adherence per month demonstrated significant differences between nVNS (n=138) and sham (n=140) for outcomes including reduction in migraine days (2.27 vs. 1.53; p=0.043). In patients with aura, therapeutic gains were noted as greater. Device adverse events were mild and transient. Application site discomfort was the most common adverse effect. The authors of the PREMIUM study (like the authors of the PRESTO study) offered that the active sham may have affected achieving significance for the primary outcome, pointing to the Schroeder (Schroeder, 2019) that demonstrated the sham device was of sufficient stimulus to activate vagal informed trigeminal pathways. However, the PREMIUM II trial with an inactive sham did not achieve significance for the primary outcome, but this study results may have been confounded by the COVID pandemic that led to decreased enrollment and participant completion.

The PREMIUM II study was initially powered to randomize 400 participants, but the COVID pandemic resulted in prematurely closing enrollment at 336 where 231 were randomized but only 113 completed the study (active, n=56 and sham, n=57). This time, the efficacy endpoints followed IHS criteria for neuromodulation trials. The sham was changed to be an inactive device. Results demonstrated a decrease in the mean number of monthly headache days from the run-in period to the last four weeks of double blind period (IHS primary endpoint) in the nVNS group (3.12) vs sham (2.29), but did not reach significance. The (IHS) secondary outcome responder rate (greater than a 50% reduction in the number of migraine days per month) was significantly higher (p = .0481) for the nVNS participants 44.87% vs 26.81% for the sham group. Quality of life, as measured by the HIT-6 (Headache Impact scale), significantly improved by -4.9 points in the nVNS group vs. -2.3 for sham (p = .025). Looking at the subgroup of participants who experienced migraine with aura, the number of headache days significantly decreased by 5.52 days (p=.0411) in the nVNS group (n=16) vs 2.74 in the sham group (n=19) demonstrating a therapeutic gain of >100% for the nVNS group. Again, like the first PREMIUM study, patients who had migraines with aura seemed to be more responsive to nVNS. No serious device-related adverse events were reported, and a greater percentage of the nVNS group were satisfied with their treatment vs sham (53.8% v 21.8%; p = .0006). Although the primary endpoint did not achieve significance (mean change in the number of migraine days from the run-in

period to the last 4 weeks of the double-blind period), clinically meaningful, statistically significant differences were demonstrated for multiple endpoints favoring nVNS including the ≥50% responder rate, change in number of headache days (aura subgroup), as well as changes in HIT-6 and MIDAS (migraine-related disability scores).

Of the transcutaneous electrical stimulation devices, nVNS has the most robust "bench to bedside" research proving the mechanism of action for vagal nerve stimulation in the treatment and prevention of migraine. Preclinical data in animal and human studies support the conclusion that activation of the vagus nerve directly impacts migraine pathways including suppression of CSD.[58] The suppression of CSD is of interest and has played out in the nVNS studies where migraine with aura seems to be more responsive to the preventative treatment. In addition to the trigeminovascular system's trigeminal, occipital, and cervical afferents, the vagal afferents also converge at the trigeminal cervical complex (TCC) sharing subcortical and cortical pathways. Collectively, investigations have shown that activation of the vagus nerve facilitates central inhibition through the trigeminovascular system, suppresses nociceptive activation of trigeminocervical neurons, and reverses cortical glutamate elevations, in addition to suppressing CSD.[59, 60, 61, 62, 63]

External trigeminal (V1) nerve stimulation (eTNS): Cefaly™

The first FDA approved noninvasive neuromodulation device was Cefaly. It received clearance in 2014 for the prevention of migraine in adults with and without aura and was expanded to acute prevention in adults with migraine with and without aura in 2017, and is CE marked for the same. Currently, Cefaly has an ongoing pregnancy register tracking safety and efficacy, but has not published their data yet. The FDA cleared recommended treatment for aborting migraine with Cefaly is 60 mins (the commercial device is set to render treatment for this duration) and 20 mins for prevention. However, the more robust clinical data was not proffered until 2022 for acute treatment in adults (as discussed below) examining 120 mins for aborting migraine. At first, Cefaly was available only by prescription in the US; it is now available without a prescription in the US and Europe.[64] The device operates through proposed external trigeminal nerve stimulation (eTNS), targeting the supraorbital and supratrochlear nerve pathways associated with migraine. However, the mechanism of action for aborting or preventing migraine has not been confirmed.

How the device works:

This rechargeable, wireless electrode device is applied to the forehead using an adhesive pad and is designed to stimulate the supratrochlear and supraorbital nerves bilaterally. The wireless Cefaly[65] has a button to activate it. Now, it can also be Bluetooth enabled with an optional application (CeCe) for choosing a treatment mode (abort or prevent), controlling intensity level, tracking migraines, symptoms, and treatments. The CeCe application is free to all to use (with or without the device) and, for those that use the device, a Cefaly coach is available 24/7 free by phone. The self-adhesive attachment needs to be replaced when the adhesive no longer works; the frequency of replacement depends on use and care (@15-20 applications). The number of uses largely depends on how the electrodes are stored and utilized. Currently, one charge of the device's LiPo battery can support up to seven acute treatments or twenty preventative sessions.

The FDA cleared duration of treatment is 60 mins for acute and 20 mins daily for prevention. The recommended treatment session by the manufacturer is 60-120 mins based on the TEAM study (see below). The acute setting uses high frequency pulses; the preventive setting uses low frequency pulses both of which are constant current generator for a maximum skin impedance of 2.2 kOhms delivering rectangular biphasic symmetrical pulses of 250 μs with zero electrical mean and a width that induces

paresthesia.[66] The high frequency pulses are 100 Hz; the intensity increases linearly to reach a maximum of 16 mA after 14 mins and then remains constant for 46 mins (for a total of 60 mins) for acute treatment. The low frequency pulses are 60 Hz; the intensity increases linearly to reach a maximum of 16 mA after 14 mins and then remains constant for the remaining 6 mins for prevention.[67] The important caveat to the programmed therapeutic max intensity level is that the patient can change the level of intensity and may not achieve the clinically validated stimulus intensity. For people who are receiving onabotulinumtoxinA injections, the device should not be used within 72 hours of an injection.

Key Clinical Evidence

As indicated above the most recent clinical trial published in 2022[68] the TEAM study (Trial of eTNS for the acute treatment of migraine) investigated 120 mins for aborting migraine with and without aura in adults. The TEAM study is the largest of the Cefaly eTNS published investigations (IIT N = 538). It relied on IHS criteria for pharmaceutical study design including primary and secondary outcomes but did not include a baseline or open label period as it was not a consistency trial design. There was a two-month treatment period conducted at 10 centers in the US. This industry-sponsored investigation was a prospective, double-blind, randomized, and sham-controlled study enrolling adults with episodic migraine of moderate to severe intensity 2-8 times per month. Participants were instructed to self-administer treatment within four hrs of migraine onset or within four hrs of awakening with migraine headache. Both the device and the sham used identical rectangular biphasic symmetrical pulses of 250 μs, with a width that induced paresthesia. But the sham frequency was 3 hz versus the eTNS frequency of 100 hz (which does match the commercial device frequency for aborting migraine). Both ITT and per-protocol (PP) analysis were used, where the ITT participants (n=538) were the randomized population who received any duration of sham or eTNS treatment; and the PP population (n=438) consisted of those who completed at least 60 mins of treatment. The primary outcome was pain-freedom at 120 mins which is the same length of time for the treatment protocol in this study.

ITT analysis (eTMS, n = 259; sham, n = 279) demonstrated pain freedom at two hrs was significantly higher (25.5% eTNS vs 18.3% sham, p = 0.043) with a therapeutic gain of 7.2%. For the secondary outcomes, pain reduction at two hrs was significantly higher (69.5% eTNS vs 55.2% sham; p = 0.001) with a therapeutic gain of 14.3%. Sustained pain-freedom (22.8% vs. 15.8%, p=0.039) and pain-relief at 24 hrs was statistically higher (45.9% eTNS vs. 34.4% sham, p = 0.006). Also, resolution of the most bothersome migraine-associated symptoms were significantly higher (56.4% eTNS vs 42.3% sham, p = 0.001) and absence of all migraine-associated symptoms at two hrs was significantly higher (42.5% eTNS vs 34.1% sham, p = 0.044). The use of rescue medications was allowed starting at 2-24 hrs after the eTNS treatment and there was no difference in rate of use between the two groups. There were no serious adverse events. Most users reported only mild discomfort, such as a tingling sensation where the device is applied.

Overall, the TEAM study supported safety and efficacy. The FDA cleared and CE mark treatment time period for aborting migraine with Cefaly is 60 mins and the device is set to render treatment this way. A patient has the option to run the 60 min cycle sequentially. There is no data from this study for treatment duration equal to or less than 60 mins as the PP analysis required at least 60 mins or more. Under the PP analysis treatment of at least 60 mins did still meet statistical significance for all the outcomes, and there was higher compliance in meeting at least 60 mins versus the full two hr research protocol. Important to note is that the study device did not permit changing the intensity level; the clinical device does.

Additional Evidence and Supporting Studies:

Regarding the safety and efficacy of acute treatment of migraine with Cefaly using the clinical protocol of a 60 mins session, there are a host of pilot and open label publications that led to FDA approval in 2014. Only one small RCT (N=109) called the ACME study (Acute migraine therapy with external trigeminal neurostimulation) looked at the 60 mins protocol and was published in 2019.[69] This industry-sponsored investigation was a double-blind, randomized, sham-controlled study conducted across three headache centers in the US (Yale, Columbia of NY, Rowe Neurology Institute). There was no run-in period and, in fact, enrollment recruitment was at the time of a participant presenting as a patient with at least 3 hrs of migraine who had not used any acute medications within 3 hrs before enrollment. Thus, neither the study design nor the inclusion criteria followed IHS guidelines but did include the IHS exclusion of treatment with botulinum or supraorbital nerve blocks in the prior 4 months, as well as opioids. Participants were randomized to eTNS (n=52) or sham (n=54). The eTNS stimulus paradigm was the same as the clinical device (but with no ability to change the intensity) and the sham stimulus paradigm was the same as the sham in the TEAM study (detailed above). Use of migraine rescue medications was not permitted for a 2 hr period from the beginning of the treatment to one hr after. The primary outcome was not according to IHS criteria (pain-freedom at 2 hrs), but pain reduction at 1 hr.[70] In fact, the authors specifically stated that they did not want to assess pain-freedom (ability of eTNS to abort a migraine), only reduction. Instead, pain-freedom was denoted as exploratory measures at 1, 2, and 24 hrs as well as pain reduction >30% and >50%. Primary outcomes also included pain score changes at 2 hr and 24 hrs. Secondary outcomes were rescue medication use at 2 and 24 hrs.

For the primary outcome (pain reduction at 1 hr) both eTNS and sham demonstrated statistically significant reductions within groups ($p < 0.0001$ for both), and there was a significant difference ($p < 0.0001$) between groups favoring eTNS (-3.46 ± 2.32, -59%) vs sham (-1.78 ± 1.89, -30%). For the 2 hr pain reduction outcome, again both eTNS and sham demonstrated statistically significant reductions within groups ($p < 0.0001$ for both), and there was a significant difference between groups favoring eTNS (-50% eTNS vs -32% sham; $p = 0.026$). Interestingly, the mean pain score reduction in the eTNS group was lower at the 1 hr assessment (-59%) than at the 2 hr assessment (-50%); in the sham group, the mean reduction was -30% at 1 hr and -32% at 2 hrs. The decrease in response in the eTNS group at 2 hrs led the investigators to speculate that a longer treatment period (2 hrs vs 1hr) may be needed. The sham continued to show an increasing reduction in pain at 24 hrs (-40%) as well as eTNS (-57%) but the eTNS was statistically significant at 24 hrs ($p=0.037$). For the secondary and exploratory measures, there was a statistically significant difference: in pain-freedom favoring eTNS, but only at 1 hr, not 2 or 24 hrs; and in pain reduction >30% and >50% at 1 hr, but not 2 or 24 hrs. Overall, participants with migraine without aura benefited more than those with aura with the eTNS. There was no difference in acute medication use. No serious adverse events. Minor adverse effects were minimal and notable for intolerance to the device (both eTNS and sham) due to paresthesia.

Regarding preventative treatment, there are three published RCTs examining the safety and efficacy of Cefaly for treatment of migraine with and without aura in adults.[71, 72, 73] The first of these is the 2013 PREMICE trial (PREvention of MIgraine using CEfalyl), which was the first clinical trial of noninvasive neuromodulation of migraine that ultimately led to the first FDA approval of a migraine noninvasive neuromodulation device.[74] The PREMICE study was a prospective, multicenter, double blinded, randomized, and sham-controlled trial conducted at 5 Belgian tertiary headache clinics run by the Belgian Headache Society. Candidates were excluded if they had received a preventive antimigraine treatment in the previous 3 months. There was a 1 month run-in period and a 3 month treatment period where 67 participants were eligible and randomized for the treatment period (eTNS, n=34 and sham, n=33) with an ITT analysis and per-protocol (PP) analysis. The eTNS device settings matched the clinical stimulation

parameters with a 250 μs pulse width, 60 Hz frequency, and 16 mA maximum intensity. The sham device settings were 30μs pulse width, 1Hz frequency with a 1mA max intensity. During the 90-day treatment phase, all participants were instructed to use their device (eTNS or sham) for 20 mins daily (like the clinical protocol). Primary outcome measures were in line with IHS endpoint criteria: change in monthly migraine days and 50% responder rate between baseline and the third month of treatment. Secondary outcomes included change in monthly headache days and reduction in acute anti-migraine medication.

For the primary outcome, change in monthly migraine days (between baseline and the third month of treatment), both the ITT and PP analysis found a significant difference within groups for both eTNS and sham, but no statistically significant difference between groups. For the 50% responder rate primary outcome, there was a significant between groups difference for eTNS vs sham under both the ITT and PP analysis (ITT: 38.2% vs 12.1%, respectively, p = 0.023). There were additional clinically notable secondary outcomes with significant differences (both ITT and PP analysis) in favor of eTNS including monthly migraine attacks (ITT p = 0.044, PP p = 0.028), monthly headache days (ITT and PP, p = 0.041), and monthly acute anti-migraine drug intake (eTNS 36% vs sham 0.5%, p = 0.007). There were no significant adverse events in either group.

Though the primary outcome change in migraine days per month between groups did not reach statistical significance in the original analysis, post-hoc analysis of the PREMICE data revealed that the response to treatment and effect size was directly related to the number of migraine days during the baseline period.[75] Under this data construct, change in migraine days per month was statistically significant between eTNS and sham.[75] The investigators pointed out in their addendum letter that this indicates eTNS may be more beneficial to those with more frequent attacks, and that the therapeutic gain of eTNS (26%) is within the range of those reported for other preventive pharmaceutical treatments. This is a common thesis for other neuromodulation devices -- that they match or surpass efficacy of pharmaceutical treatments for aborting and preventing migraines.[8, 9] Additional open-label and Real Word Evidence (RWE) investigations support the safety of the Cefaly device,[76, 77, 78] patient satisfaction,[77,78] that consistency is important for therapeutic effect;[79] and, that Cefaly may be an option for refractory migraine.[79]

Cefaly's mechanism of action has not been investigated in relation to the predominant validated migraine pathways, but two interesting investigations looked at brain neurophysiological changes from eTNS using imaging, FDG-PET[80] and fMRI.[81] The FDG-PET scan study examined differences in participants with episodic migraine without aura (n=14) that were eTNS naive compared to healthy controls (N-20). The migraine group was scanned at baseline (before any stimulation, PET1), immediately after a 60 min session of eTNS (PET2), and after three months of daily 20 min eTNS therapy (PET3). The healthy controls were scanned only at baseline. The investigative device used the same stimulation parameters for prevention as the commercial device. Baseline analysis (PET1) revealed that the migraine participants (n=11) were significantly hypometabolic compared to controls (n=20) in fronto-temporal regions (threshold: $p<0.001$ *uncorrected,* 20 voxels) particularly the orbitofrontal cortex (OFC) and rostral anterior cingulate cortex. PET2 did not result in changes for the migraine participants compared to PET1, but at the end of the 3 month treatment period for migraine participants that had at least 30% compliance (n=10), metabolism in fronto-temporal regions significantly increased particularly the OFC (pFWEcluster=0.001) comparing PET1 to PET3. Though interesting results - that the BOLD signal increased in these regions that were previously hypometabolic compared to controls - the small size and no sham control limits conclusions that can be drawn.

The whole brain fMRI prospective study investigated heat response of the trigeminal nerve (V1) in adult migraine patients without aura (n=20) vs controls (n=16). A baseline fMRI was obtained for migraine and control participants, looking at correlated heat response and pain perception (using a Visual Analog Scale).

After 60 days of eTNS treatment for 20 mins/day using the Cefaly, migraine participants underwent an additional fMRI session with heat response testing (not controls). The baseline fMRI comparison between the controls and migraine participants before treatment did find higher noxious levels of heat (51°C vs 41°C) in migraine participants' right anterior cingulate cortex (ACC) perigenual part had a greater BOLD response. After 60 days of eTNS treatment, the same area demonstrated a significantly reduced BOLD response in the migraine participants ($p = 0.008$) and per the investigators suggested "normalization". But there was no control comparison or sham comparison; thus, no meaningful conclusions could be drawn from this result. The investigators also measured multiple migraine severity parameters after the 60-day treatment period and found significant decreases in frequency of monthly migraines, number of migraine days, mean pain intensity, and reduction in daily life disability as measured by the Headache Impact Test (HIT-6) scale. The authors included in their discussion an exploratory correlation analysis where they found a significant negative correlation between the change in ACC BOLD response to heat stimulation and the frequency of attacks both before *and* after eTNS treatment. Given the small size of the study, limited control comparisons, and no sham intervention, this study offers limited supportive evidence of clinical improvements with eTNS, and that there is some effect of consistent eTNS treatment on ACC BOLD response to heat stimuli. It does not provide any insights into the direct relationship between the effects on brain function and changes in migraine characteristics as a result of eTNS treatment.

Finally, the most commonly reported side effect of Cefaly is sleepiness during a treatment session and sedation after treatment. This effect was explored in non-migraine participants in a small double-blind, cross-over, sham-controlled study on 30 healthy subjects looking at the effect of both low and high frequency stimulation on vigilance and attention.[82] Only the high frequency stimulation demonstrated a significant effect on these psychophysical tests with decreased vigilance and attention. This may be relevant in understanding the results of the abortive eTNS clinical studies discussed above. The studies used either a 60 min or 120 min treatment session where the primary outcome (pain-freedom) coincided with the treatment length. The initial preclinical research of neuromodulation for pain and migraine found that concordant paraesthesia of the stimulated pathway (V1 trigeminal or occipital, as discussed below) had to be achieved for therapeutic effects.[83] For Cefaly (and as discussed below for Relivion), achieving the therapeutic minimum intensity, and some degree of paraesthesia, is needed to achieve therapeutic effect. Taken together, an important consideration arises with the eTNS device Cefaly (as well as Relivion): is the therapeutic effect in migraine patients due more to changing attention to abort migraine than directly affecting migraine pathophysiology, or is there some other mechanism of action? The mechanism of action for both devices is probably multifactorial and could include multiple pathways such as central pain inhibition through release of endogenous opioids or descending pain inhibitory pathways, all of which are dependent on a number of factors when delivering an electrical current transcutaneously including local skin impedance, pulse width, frequency and intensity of the current, length of treatment, and frequency of treatments.[84, 85]

Combined Trigeminal (V1) + Occipital nerve stimulation (eC-TONS): Relivion™

The noninvasive neuromodulation device Relivion combines trigeminal (V1) and occipital nerve stimulation (eC-TONS) and was FDA approved in 2021[86] for acute treatment of migraine with and without aura in adults. Though previously CE marked, currently it is only available in the US. The parent company[87] intends to expand availability. The headset integrates two sets of electrodes. One set contacts the forehead (two bilaterally, for a total of four) and the other set contacts the occiput (two electrodes bilaterally) in order to stimulate both the trigeminal V1 (presumably supraorbital and supratrochlear branches) and greater occipital nerve branches, respectively. As discussed above, a pivotal interface of nociceptive afferents from both the trigeminal nerve and the greater occipital nerve converge on the same second-order neurons in the TCC, and share final common pathways to subcortical and cortical structures involved in migraine pain,

somatic triggers, and modulation. The earliest investigational trial with combined trigeminal and occipital stimulation was a case series (n=7) completed in 2009 using implanted leads in participants with chronic refractory migraine who were severely impaired by their pain.[88] All participants had either complete resolution or significantly reduced frequency and pain severity with full return to function. The investigators pointed out that some migraine patients have an occipital focus where the migraine pain is perceived more so, or primarily, in the greater occipital nerve distribution (like secondary headaches such as occipital neuralgia or cervicogenic headaches) rather than principally trigeminal distribution. They also showed that combined stimulation of both the trigeminal (V1) and occipital pathways was required to achieve therapeutic effect.

This case study series specifically led up to the development of Relivion. Being the newest of the transcutaneous electrical stimulation device, and only having received FDA approval in 2021, there are limited clinical trials, RWE studies, and post-marketing information. But it stands on robust pre-clinical data[89] and on acceptable clinical trial evidence, thus far. The Relivion device is currently undergoing additional clinical trials for migraine prevention[90] as well as for anxiety and depression.[91]

How the device is used:

Before using the battery-powered, rechargeable device for the first time, the adjustable light-weight headset (90g), must be properly fitted as instructed through an online or smartphone tutorial. The device does not require but does have an associated Bluetooth enabled application.[92] The device user-interface allows the patient to turn it on and off and to adjust the stimulation intensity. The application does not turn the device on or off or change the intensity of stimulation, but if in use it shows the intensity level and provides a timer. Range of intensity settings are from 1 (the lowest) to 100 (the highest). Upon activation, the treatment automatically runs and ends after 60 mins. The user has the option to stop the treatment earlier. The FDA approval is for 60 mins for acute migraine. However, the Relivion website and user manual suggest that patients can select 20-60 mins of treatment and notes that there is no limit to repeat uses. The website and manual do caution patients to limit treatment to 80 mins/day as prolonged treatment "may cause skin irritation".[93] The user manual recommends increasing intensity if the patient feels the sensation weakening. It states that patients should feel the stimulation is strong but not painful. Before placing the headset on for each treatment, the patient must first wet the six single-use electrode pads.[94] There are four frontal and two occipital. There is a nose bridge to stabilize the device. Once on, the patient must press the back electrodes closer to the scalp until they feel the moisture. The application can walk the patient through all the steps needed to prepare and use the device. For people who are receiving onabotulinumtoxinA injections, the Relivion device should not be used within 72 hours of an injection.

The Bluetooth-enabled application also has a migraine and treatment tracking diary, as well as tutorials on how to use the device and basic information on migraine. Patients can also enter migraine and treatment information including descriptions of their migraine and treatment effects. When using the Bluetooth function, the application automatically documents treatment use (frequency, intensity level, and duration) and transmits encrypted data via the internet to the iCloud prescribing physician dashboard (if they are a registered user). A texting communication function in the application allows the prescriber to make treatment recommendations. The application provides the patient with statistics (based on the last 6 months of use) regarding: headaches per month; percent of treatment with pain relief per month; total number of medication use days per month; trigger distribution; and area distribution of migraine pain (front right, left, or back of the head). This data is also accessible to the prescriber on their dashboard. The device is available by prescription only.

The stimuli parameters of the clinical device are: frequency 80 hz phase rise 5 μS, ramp modulation hence max intensity controlled by patient but the max amplitudes are for frontal 6mA and occipital 12mA. The most common reported adverse include temporary scalp numbness, tingling, pain, skin reaction, and headache in addition to treatment and post-treatment sedation, fatigue, and sleep disruptions. Sedation and fatigue are also commonly reported with the Cefaly device and, as discussed above, may contribute to the therapeutic effect.

Key Clinical Evidence:

The industry-sponsored Relivion in Migraine (RIME) study examined safety and efficacy for the treatment of episodic migraine with and without aura in adults (N=131).[95] The RIME study was a prospective, randomized, double-blind, sham-controlled, multi-center clinical trial at 12 sites in the US and Israel. Unfortunately, the COVID-19 pandemic led to early termination of the trial. However, FDA guidance was followed for completing the study and analysis. There was also a technical issue with the active-device[96] that was resolved with approved enrollment of additional participants and elimination of data from the defective device. This did not impact blinding and, despite early termination and reduced enrollment, the study met its primary endpoint.

There were two phases: a 28-day run-in (in which all participants kept a migraine diary and had to remain stable on preventative and rescue medications) and a treatment phase. There was no open-label period or consistency phase in this study. Main exclusion criteria included onabotulinumtoxinA treatment (head, neck, face) 3 months preceding screening, and supraorbital or occipital nerve blocks 1 month preceding screening. The investigational device was identical to the commercial device: symmetrical biphasic waveforms with phase duration of 330– 400 ms at an 80-Hz pulse frequency and peak intensity 6 mA for the bilateral V1 trigeminal branches (bilateral supraorbital/supratrochlear) and up to 12 mA for the bilateral greater occipital nerves. The sham device was identical to the Relivion delivering a stimulation above the sensory threshold to aid with blinding using symmetrical biphasic waveforms with phase duration of 70–100 ms, 0.33- Hz pulse frequency and peak output current of 5 mA for the trigeminal branches and up to 10 mA for the occipital nerves. The investigational protocol was the same as the clinical treatment protocol: participants were to treat for the full 60 mins duration, but they were included in the study if they treated at least 30 mins. Participants were instructed to treat "at attack onset"[97] as soon as possible and within 30 mins of onset. Both devices allowed for changing the total treatment time and intensity delivered.

To be further eligible for the treatment phase of the study, all participants had to self-administer 1-2 treatment sessions at a minimal intensity of 2 mA for a minimum of 30 mins. Failure to administer at least one treatment as such and complete the diary resulted in exclusion from the treatment phase and analysis. No rescue medications (or cannabis) within 2 hrs of treatment initiation were to be used. Participants who did take rescue medications before 2 hrs were considered treatment failures. For a study treatment to be eligible for analysis, more than 48 pain-free hrs had to have passed since the previous migraine episode and no rescue medication or cannabis product use within 4 hrs before treatment initiation. Also, migraines upon waking were excluded (and not to be treated). The primary outcome was not pain-freedom as recommended by IHS, but pain-relief 2 hrs post-treatment initiation (defined as reduction of migraine headache pain from severe or moderate to mild or no pain, or from mild to no pain). Secondary outcomes were pain-relief at 1 hr and pain-freedom at 2 hrs. Exploratory endpoints included sustained pain-relief and freedom at 24 hrs, and freedom from most bothersome symptoms (MBS) at 2 hrs. End point analysis was performed on data from the first eligible treated migraine. Safety analysis was conducted on the ITT population. Efficacy analysis on the modified ITT (mITT) dataset was defined as all participants who treated at least one eligible migraine.[98]

Of 131 ITT participants (n=67 active, n= 64 sham), 109 treated at least one migraine episode (mITT: n= 50 active, n= 59 sham). Under the mITT analysis the study met all primary and secondary efficacy endpoints and demonstrated superiority in all but one exploratory endpoint (sustains pain-freedom at 24 hrs). The active arm experienced without use of rescue medication greater relief at 1, 2, and 24 hrs ($p = 0.012$, $p < 0.001$, and $p = 0.031$, respectively); pain-freedom at 1 and 2 hrs ($p < 0.001$ for both) but not 24 hrs; and freedom from MBS at 2 hrs ($p = 0.047$). Freedom from MBS is notable, as the only other noninvasive neuromodulation devices that have demonstrated superiority in adults in this regard, thus far, are the Cefaly and Nerivio.[99] The RIME study also found a significant increase in active participants reporting both pain and MBS freedom at 2 hrs vs sham ($p < 0.001$).

Also notable in this study is that after the first eligible treatment, significantly fewer participants ($p = 0.015$) in the active group (14/48, 29%) reported use of rescue medication versus sham (30/57, 53%). In the other noninvasive neuromodulation studies reviewed in this chapter, there was no difference in rescue medication use between groups. Findings such as these in the RIME study are important as there is increasing recognition of the clinical utility of noninvasive neuromodulation as an adjunct to avoid medication overuse headaches and the adverse effects of oral medications (both OTC and prescription). Finally, there were no serious adverse events and only a few mild adverse events (scalp numbness, mild pain, skin redness, tingling, twitching, migraine) that were transient and resolved.

Additional Evidence and Supporting Studies:

Before the RIME study that used the currently available Relivion device, two smaller prospective sham-controlled, double-blind RCTs looked at safety and efficacy using prototype devices; these studies were not peer-reviewed.[100] The conclusion from these trials was that the prototype devices were safe and efficacious. The same year the RIME study was published, a small single center[101], prospective sham-controlled, double-blind RCT (n=27 active, n= 28 sham) investigated Relivion for aborting migraine in *both* episodic and chronic migraine in adult participants.[102] The device again proved to be safe and tolerable. Though pain relief and freedom were higher in active vs sham at 1, 2, and 24 hrs, it was not statistically significant. But, for those with baseline moderate-severe pain at the time of treatment, pain-freedom at 2 hrs was significantly greater compared to sham (42.86% vs. 10.53%, $p = 0.02$). VAS score change at 1, 2 and 24 hrs as a secondary outcome did demonstrate a statistically significant difference in favor of the treatment group ($p = 0.0002$, $p = 0.0324$, and $p = 0.0220$, respectively). The authors of this investigation propose that, like invasive combined trigeminal and occipital stimulation, eC-TONS may be more effective than single channel eTNS when comparing their results to the ACME study (discussed above) for eTNS.[103] Although interesting to consider, without a head-to-head study this remains speculative.

Remote Electronic Neuromodulation (REN): Nervio™

Nerivio is FDA cleared and has a CE mark for both acute and preventative treatment of migraines with or without aura in adults and adolescents 12 or older. In November 2024 it received FDA clearance for acute and preventative treatment for pediatric patients starting at age 8; it is the only non-invasive neuromodulation device for pediatrics at this time. Nerivio is a wearable system that delivers a transcutaneous current through an arm band that is remotely activated using a technique known as Remote Electrical Neuromodulation (REN). The armband is Bluetooth-enabled using a smart-phone REN application. The proposed therapeutic effect of Nerivio is through conditioned pain modulation (CPM).[104, 105] The arm band provides a sub-pain-threshold stimulation theoretically of Aδ and C-fibers activating top-down central pain inhibition that modulates the intensity of migraine pain during an acute attack and potentially the response to migraine triggers. This hypothesized mechanism of action has not been formally tested and

confirmed.[106] Notwithstanding confirmation of the postulated mechanism of action, the device has clinical and reasonable real word evidence regarding its safety and efficacy.

How the device is used:

Nerivio is a wearable, self-administered system that delivers a transcutaneous current through a lightweight, adjustable band worn on the upper part of the arm. It is available by prescription and is remotely activated by a bluetooth-enabled smart-phone application.[107] The current is a patented biphasic rectangular waveform delivered via a single channel at a modulated frequency of between 100Hz and 120Hz, with a 400μs pulse width and an output current of up to 40mA. A treatment session to abort a migraine lasts 45 mins and the length of time is controlled by the application. Treatment to abort should be started ideally within 60 mins of onset of aura or migraine pain. For aborting a migraine, it can be used as often as needed and there is no limit on use. However, Nerivio is a disposable device limited to 18 treatment sessions of 45 mins. Preventative treatment is 45 mins every other day. The application has a refill function.

Using the application, the treatment intensity can be controlled by the patient using a scale of 0-100, though the clinical-trial effective intensity is at least level 20 (the application reminds the patient of this). There is an 'abort' button to pause or stop treatment. The application also allows for tracking use, headache days, symptoms, functional disability, and medication use using a "diary" and will provide analyses of these data to the user. Data can be shared with the prescriber by exporting the diary. There is no data-protected transmission system with the device or platform for sharing with a prescriber. The software can be set to provide reminders for preventive therapy, and the application will produce reminders that are generated from the data analysis such as encouraging the patient to use the device as soon as symptomatic. The application has additional features such as guided education and relaxation techniques. The smartphone-controlled features of Nerivio may enhance user engagement and adherence in younger populations; however, it may present challenges for older adults and those less familiar with technology. The device cannot be used without a smart-phone.

Key Clinical Evidence

Following a pilot study in 2017 demonstrating safety and efficacy in aborting episodic migraine in adults with and without aura,[108] the pivotal study was completed in 2019.[109] This industry-sponsored investigation (N=252) was a prospective, randomized, double-blind, sham controlled, multi-center trial at 7 sites in the USA (N=175) and 5 sites in Israel (N=77). In addition to meeting IHS criteria for episodic migraine, to be eligible for the study participants had to be either on no preventative medications or stable on preventative medications two months prior to recruitment. There were two phases: a 1 month run-in period and a treatment period (that ended in Oct 2018). There was no open label period but there was a consistency analysis. During the run-in phase, participants in both groups used the application migraine diary. During the one month roll-in, participants had to demonstrate the ability to use the device and application, keep the diary with the application, and remain stable on preventative medications. Those who had 2-8 attacks and completed at least 66% of their migraine diary were eligible to continue to the treatment phase (N=99 treatment, N=103 sham). Participants were excluded from treatment if they used OnabotulinumtoxinA one month prior to the treatment phase, or if they used a nerve block or an IV infusion 2 weeks prior.[110]

For the treatment period, the sham control was an electrical pulse of similar width and intensity, but much lower frequency compared to the active device. Participants in both groups were instructed to initiate treatment as soon as headache pain or aura began and no later than 60 mins from onset. They needed to complete at least 30 mins of the recommended 45 min session. A qualifying migraine attack for treatment

with the device was defined as 48 hrs of migraine freedom *prior* to treatment. Participants were also instructed not to use rescue medications for at least two hrs after the first treatment with the device. The application was used to gather data on: treatment start time in relation to symptom onset; pain level at treatment start, 120 mins after and 48 hrs after treatment start; associated symptoms during the attack (nausea, vomiting, photophobia, phonophobia, and allodynia) collectively analyzed as most bothersome symptoms (MBS); response to treatment; and rescue medication use.

The primary outcome was the proportion of patients with pain relief at 2 hrs post-treatment without rescue medications. This would be an IHS secondary outcome, as pain-free is the IHS recommended primary outcome. For this study, pain-free at 2 hrs was a secondary outcome as well as MBS freedom and MBS relief. Exploratory endpoints included 48 hr sustained pain-free and pain relief responses; pain relief at 2 hrs post-treatment in at least 50% of all treated attacks; and pain-relief at 2 hrs post-treatment as a function of baseline pain level. Intention-to-treat (ITT) population included all the participants who underwent randomization and was used for safety analyses. The first reported treatment was considered a 'training" treatment and was only included in the safety analyses. Efficacy analyses were conducted using a modified intention-to-treat (mITT) population and included: all randomized participants who had performed a "test" treatment (distinct from the "training" treatment and defined as those who treated within one hr from symptom onset); completed at least 35 mins of treatment; and were pain free 48 hrs before the test treatment.

The device proved to be both effective and safe in this study. For the primary outcome, active stimulation was more effective than sham in achieving pain relief at 2 hrs [66.7% (66/99) vs 38.8% (40/1030); p = 0.0001)] with a therapeutic gain of 27.9% [CI 15.6-40.2]. For the secondary outcome and exploratory analysis, at 2 hrs post treatment, active device participants achieved greater pain-freedom (37.4% vs 18.4%, p = 0.003), and MBS relief (46.3% vs 22.2%, p = 0.0008), but there was no difference with MBS freedom between groups. The proportion of participants who achieved both headache and MBS relief at 2 hrs post-treatment was superior in the active group (40.0% vs. 15.2%; p = 0.0004.) For all baseline pain levels at the start of treatment, active treatment was superior for pain relief. Pain relief and pain-free superiority of the active treatment was sustained 48 hrs post-treatment. Consistency analysis demonstrated that 60% of active treatment participants achieved at least a 50% reduction in pain within two hrs of using the device. The incidence of device-related adverse events was low and similar between treatment groups [((active 4.8% (6/126) vs sham 2.4% (3/126), p = 0.499)]. These events that resolved included sensation of warmth, local tingling, numbness in the arm, pain in the arm, or redness of the skin at the site of the device.

Additional Evidence and Supporting Studies:

With respect to prevention in adults, the pivotal trial is the 2023 industry-sponsored prospective, randomized, double-blind, sham-controlled, multi-center trial of adults with episodic and chronic migraines with and without aura.[111] There was a 4 week run-in phase (where participants had to be stable on a single preventative migraine medication for two months prior to enrollment), and an 8 week treatment phase (shorter than the IHS recommended 12 week period for neuromodulation clinical trials). There was no IHS recommended open label period for a prevention trial. The treatment device and protocol were the same as the clinically recommended protocol for prevention: 45 mins every other day. However, the level of intensity could be changed in this study. Participants were instructed not to use their devices for acute treatment but instead use their usual acute headache/migraine treatments. Of the 248 enrolled participants, 179 qualified for the modified intention-to-treat (mITT) analysis (95 active; 84 placebo). For the primary outcome, mean reduction in the number of migraine days per month from base-line during the run-in phase to the last 4 weeks of the treatment phase, the active group was superior to sham (p<0.001) with a therapeutic gain of -2.7 migraine days (CI95% -3.9, -1.5). For the main secondary endpoints, mean change in number of

moderate-severe headache days and change in headache days per month (comparing the baseline to the last four weeks of treatment phase), the active group was superior to sham ($p = 0.005$, $p<0.001$, respectively) with a therapeutic gain of -2.69 headache days/month (CI95% -3.87, -1.51). Also, there was a statistically significant reduction in the active group of acute headache/migraine medication-use days ($p = 0.001$) with a therapeutic gain of -2.08±0.63 days [CI95% (-3.33, -0.83)]. The active group was superior to sham in reducing by least 50% the number of headache days from baseline for all headache severities (26.3% vs 1.9%) as well as for moderate/severe headache days (51.6% vs 35.7%, $p = 0.033$). The investigators also looked at change in function as measured by HIT-6 and the Migraine Specific Quality of Life Questionnaire, but there was no difference between groups. There were two serious adverse events deemed unrelated to the treatment device (suicide attempt and appendicitis), and one sham non-serious adverse event. Otherwise, there were no serious device-related events, and treatment was tolerable and safe. There was no statistical difference in participants identifying which treatment they received. Device use was tolerable, 89.8% of participants in the active group completed more than 75% of the per-protocol number of treatments.

Overall, safety was re-confirmed using Nervivo and efficacy for prevention. Of note, this study did allow for onabotulinumtoxinA and CGRP mAb injections for prevention, provided that treatment had been stable for at least 2 months according to IHS guidelines. However, whether a participant had received such preventatives at the start of the trial was not documented, nor were additional treatments monitored. Hence, the shorter 8-week treatment period of this study was not ideal for parsing potential baseline preventative medication effects. The IHS clinical trial neuromodulation criteria recommends a minimum12-week treatment period with ideally a total of 24 weeks to assess changes from baseline. Although the authors included a post-hoc analysis from which they concluded there was a trend to greater improvement treatments in participants who did not take preventative medication, they did not specify if this was for only the treatment group or both groups. In addition, the definition as presented in the publication for 'migraine day' was not in accordance with IHS criteria. These limitations are acknowledged by the investigators.

Nerivio is not per se contraindicated in pregnancy and has not been prospectively tested during pregnancy. However, Nerivio has amassed the largest data-set of any noninvasive neuromodulation device allowing for retrospective analysis regarding safety and efficacy during pregnancy. Using critical pregnancy outcomes, a retrospective case-control survey study.[112] evaluated the safety of Nerivio for migraine treatment during pregnancy through 3 months postpartum comparing women recruited from the Nerivio database (n=59) who did at least three treatments during pregnancy with women (n=81) who did not use Nerivio during pregnancy (recruited from US clinics treating pregnant women with migraine). The device was deemed safe as there were no significant differences between the two groups as to examined outcomes (gestational age at delivery, newborn weight, miscarriage rate, preterm birth rate, birth defect rate, stillbirth rate, rate of newborns meeting developmental milestones at 3 months postnatal and emergency room visits).

Because the Nerivio application has a built-in function that allows de-identified data to be gathered with a user's consent, this has enabled both Real World Evidence (RWE) and open label analysis to take place to a much more rapid degree for Nerivio compared to other devices (See Appendix A).[15] For example, the device's safety profile is consistently favorable, with side effects being mild and transient, such as skin irritation at the stimulation site.[113, 114] Efficacy in acute treatment is consistent even with 12 months of use[114] and there is data to support the effectiveness for acute treatment of migraine in those with chronic migraines.[115, 116]

For adolescents, both an open label and RWE analysis demonstrated safety and efficacy for aborting migraines: a prospective, open-label, single arm, multi-center study conducted at 12 sites in the USA;[117] and a 2023 RWE analysis of Nerivio prescribed to adolescents (n=582) at multiple US pediatric clinics to

treat acute migraine attacks.[118] Nerivio is the only device FDA approved for pediatric patients. The FDA approval for both acute and preventative treatment in ages 8 and older was issued in November 2024 and was based on a RWE analysis of children ages 6-11 (N=293, MEDIAN age 11, IQR 9-11, 73% girls) who were prescribed Nerivio off-label (for those under 12 years of age). The investigators analyzed de-identified data (5493 Nerivio treatments, 3248 of those completed by the 11 y/o group) culled from the application from all users whose parents consented to application data being used for research purposes. There were no adverse events or device adverse events, and the analysis supports that Nerivio may be effective for reduction of both pain and associated symptoms, though the extent of placebo effect cannot be determined given the lack of a control group. As presented in the introduction to this chapter, treatments for acute migraine and preventing migraine in pediatric and adolescent patients are significantly limited. The majority of randomized controlled trials studying the efficacy of preventive medications for pediatric patients have failed to demonstrate superiority to placebo. This leaves only behavioral interventions with trigger avoidance for prevention,[7] and over the counter medications for aborting migraine. Having a safe option like Nerivio would be beneficial for pediatric and adolescent patients. Long-term data would be additionally warranted not only on treatment outcomes in these populations, but any impacts on development, overall well being, and functional outcomes.

Cortical Stimulation Device - Single Pulsed Transcranial Magnetic Stimulation (sTMS)

Currently, there is only one FDA cleared hand-held, portable device that acts directly on the cortex using single pulse transcranial magnetic stimulation (sTMS), the SAVI Dual™ by eNeura.[119] This device was first approved in the US in 2014 for aborting migraines in adults and is now cleared for aborting and preventing migraine with or without aura in adults and adolescents (12 or older). The proposed mechanism of action is that sTMS disrupts CSD and aborts migraine both with and without aura.[120] Understanding the relationship between migraine and CSD is rooted in experiments that used transcranial magnetic stimulation (TMS) to induce aura like symptoms in healthy adults,[23, 24, 121] and the therapeutic potential of TMS to suppress CSD was first uncovered in animal models.[122] It was this line of research that led to the development of sTMS for migraine treatment in humans.[120] As set out in the introduction, CSD and CSD predisposition was thought to be strongly associated only with migraine with aura; now this phenomenon is also associated with migraine *without* aura as well as with photosensitivity to light during the ictal migraine and interictal cycle of migraine. CSD predisposition can sustain the brain's hyperexcitability and central sensitization to migraine and it is this sustained and provoked hyperexcitability that is targeted with sTMS to prevent and abort migraine.[120]

How the device is used:

The SAVI Dual is a rechargeable battery-operated handheld device. It weighs a little over three pounds and is held to the back of the head to deliver the sTMS; the device is designed to curve around the occiput region. It takes about one to two mins for the device to initially charge and it is discharged with a push of a button delivering a very brief (< 1s) single pulse of magnetic energy at 0.9 Tesla. The device emits a soft, audible click as the treatment is delivered and is painless. The protocol for aborting migraine is to initiate treatment at the onset of aura or migraine pain;[123] the patient is to deliver four sequential pulses. If no resolution "after a brief pause" (user manual)[124], a patient can deliver another set of four sequential pulses. There is no limit on the total number of pulses that can be delivered. For prevention, treatment is BID with four total pulses. It takes about 30-60 seconds for the device to recharge after pulse delivery.

For those who may be mobility impaired, one can lay on the device to discharge, or have a caretaker push the button. Treatment care plans can be personalized by the prescriber based on the patient's migraine characterization. The prevention protocol can be increased to three or four times a day.[125] Again, the goal of sTMS is to decrease the brain hyperexcitability and predisposition to CSD.

The device connects wirelessly via a cellular connection (US) or uses a SIM card (UK and Australia) for a preprogrammed duration of use and refills. Each patient has a clinical coordinator that assists with setting up the device and education. The clinical support contact checks in regularly and is available for troubleshooting. The manufacturing company eNeura will be re-introducing Remote Therapeutic Monitoring that is compatible with 5G cellular networks (in both the US and Europe) and newly introducing a bluetooth enabled diary application for tracking headaches, treatments, disability status, and medication use for the patient and to share with the prescriber.[126]

Key Clinical Evidence:

Several pilot studies preceded the larger RCT which examined and confirmed safety and efficacy of sTMS in treating migraine[127,128] and led to the creation of the handheld device.[129] Even though the pilot studies demonstrated safety and efficacy in aborting migraine with *and* without aura in adults, because the efficacy was 100% in migraine with aura, the investigators decided to only focus on this population for the larger RCT.[120] This pivotal industry-sponsored study[130] for aborting episodic migraine with aura in adults was a prospective, double-blind, sham-controlled, randomized trial conducted at 18 centers[131] in the US from August 2006 to February 2008.[132] There was a 1 month lead-in phase to confirm participants met inclusion criteria followed by a 3 month treatment phase, meeting IHS criteria for aborting migraine investigation. There was no open-label period but there was a consistency phase that extended three months beyond the treatment period examining the next three treated attacks, also meeting IHS criteria. Eligible individuals had to meet IHS clinical trial criteria for migraine with aura defined as visual aura preceding at least 30% of migraines followed by moderate or severe headache in more than 90% of those attacks. To be further eligible to enter into the treatment phase, during the 1-month lead-in phase participants must have had at least one migraine with aura. All participants had to be stable on their medications and could continue preventative migraine medications. Medications that could affect aborting migraine were not permitted 12 hours before treatment under this study (such as NSIADS or antiemetics) and rescue medications were not to be used until 2 hrs after attempting treatment.

Also meeting IHS criteria, the primary outcome was pain-freedom at 120 mins for the first treated attack. Secondary outcomes included pain-freedom at 24 and 48 hrs, as well as a non-inferiority analysis of secondary symptom reduction (nausea, photophobia, and phonophobia) 120 mins after the first treated attack. The study also assessed efficacy of treatment in participants who used preventative migraine medications, response to treatment based on pain severity at the time of treatment, and consistency of pain-freedom in two of three treatments with aura. The safety analysis included all participants randomly allocated to a treatment group (n=201), and a modified-intention-to-treat (mITT) protocol was used for efficacy analysis that included participants who treated at least one migraine with aura during their treatment phase (n= 82 sham v n=82). A per-protocol (PP) analysis was used for all participants who treated at least one migraine with aura, who had no missing assessments, no change in medication use, no protocol deviations, and did not use rescue drugs before the two hr assessment (n=71 sham v n=70 sTMS).

Patients were instructed to treat as soon as possible after the aura had begun and no later than an hour afterwards. All participants were permitted to treat up to three attacks. The treatment device parameters delivered a pulse of 0.9 Tesla as does the clinical device. The protocol required delivery of two pulses 30 seconds apart (the time for the device to recharge). The current clinical protocol is four sequential pulses.

Also, there were no additional treatments for an attack under the study: (The clinical protocol recommends additional treatments as needed for unresolved migraine/symptoms). The sham made the same buzzing sound and vibrated for two seconds like the device.

Under the mITT analysis for the primary outcome, at 2 hrs 39% (32/82) of patients in the sTMS group were pain-free compared to 22% (18/82) in the placebo group (p = .018) for a therapeutic gain of 17% (95% CI 3–31%; p = 0·0179). For the secondary outcomes sustained pain-freedom at 24 hrs was observed in 29% of the sTMS group versus 16% in the placebo group (p = 0.04). Stratified by mild, moderate or severe pain, moderate pain had the greatest response to treatment (p = 0.0014), though the severe sample was not included for analysis as the authors stated the sample was too small. There was no difference between sham and sTMS with respect to nausea, photophobia, or phonophobia, and the sTMS did not make any of these symptoms worse. Interestingly, prophylaxis was a significant covariate and the absolute risk reduction was greater in sTMS vs sham (32% vs 8%). Treatment was well tolerated and there were no severe adverse events. The most common adverse events reported in the sTMS group (2%) were headache, migraine, and sinusitis. Participants didn't know if they were in the sham or treatment group. The results were consistent in the three months following the treatment phase. In summary sTMS was well tolerated and proved statistically significant effectiveness in acute treatment of migraine with aura.

Additional Evidence and Supporting Studies:

The diagnostic and therapeutic effects of TMS have been investigated for over 40 years for a number of neurologic and psychiatric conditions.[120] The current sTMS portable device SAVI Dual is relatively new in the field of noninvasive neuromodulation, but the concept of sTMS for the safe treatment of migraine stands on firm preclinical and clinical ground.[133, 134] As discussed above, there were several pilot studies that established the safety and efficacy of sTMS using a table-top device in a clinical/research setting to treat migraine with and without aura.[135, 136] It was these pilots that led to the creation of the portable handheld device by the same investigators and inventors.[137] The portable device was used in the larger RCT as described above. The inventor and co-investigator, Dr Robert Fischell, hypothesized that sTMS may be an effective acute treatment for migraine[120] by disrupting CSD as shown in animal studies [122] which then led to the pilot studies of sTMS for the treatment of migraine. Again, although the pilots demonstrated safety and efficacy in migraine with and without aura, because the efficacy was 100% in migraine with aura, the investigators decided to focus on this population for the larger RCT.[120] Subsequent open label studies have supported safety and efficacy in migraine *both* with and without aura as well as patient satisfaction with sTMS. [133,138]

There is no RCT for the prevention of migraine with and without aura: there is an observational, open label study (n=263) called ESPOUSE (eNeura SpringTMS Post-Market Observational U.S. Study of Migraine) that confirmed safety and efficacy in migraine prevention[139] as well as reduction in acute medication days and HIT-6 scores. It was based on the EPOUSE study the FDA approved sTMS for migraine prevention with and without aura in adults. In addition to prevention, additional post-marketing studies have demonstrated sTMS as a viable treatment option for difficult to treat migraines[140, 141] and medication overuse headaches[142], but no RCTs have been completed to verify this.[143] With respect to adolescents, the FDA approval for acute treatment and prevention in this population was based on a small (n=12) open-label pilot that demonstrated feasibility, safety, and tolerability (Irwin, 2018).[144]

Drs. Anna Andreou and Jospeh Lloyd of the King's College of London have provided critical investigative insights into the mechanism of action of sTMS in treating migraine in addition to clinical trial data. Their

research substantiated the treatment effect is suppression of CSD.[145, 146] They have also demonstrated that, in addition to CSD suppression, sTMS has substantial effects on cortically connected subcortical nuclei[145] which are important in the trigeminovascular system pathways. Specifically they looked at sTMS's effect on trigeminovascular activity of second order trigemontothalamic and third order thalamocortical neurons in rats and found that it significantly inhibited both spontaneous and evoked firing of the third order thalamocortical neurons.[145] This suggested, according to the authors, an additional potential migraine modulatory effect of sTMS. Drs. Andreou and Lloyd continue to collect evidence regarding the mechanism of treatment effect of sTMS using animal models; they believe sTMS increases CSD threshold activation and inhibits both spontaneous and glutamate induced cortical neuronal activity.[147] Like nVNS, sTMS treatment for migraine has robust bench-to-bedside data supporting this noninvasive neuromodulation modality as safe, effective, and clinically rational.

Choosing a Noninvasive Neuromodulation Device

See Comparison Tables at end of guide.

Selection of a device can be challenging as they act on different proposed migraine pathways and have unique treatment protocols. Using the IHS clinical design criteria to weigh safety and efficacy and applying patient characteristics with the following guidelines may help with device selection.

Is the device obtainable and affordable?

Unfortunately, device availability remains a considerable barrier as most payors in the US do not cover the prescription devices except for the Veterans Administration which covers all of them (including Cefaly). Cefaly must be paid for by other patients. As presented throughout this chapter several analyses have shown that out-of-pocket cost for the prescription devices in fact may be far less than the cost of prescribed oral medications even *with* insurance coverage, particularly considering expenditures over time (Harris, 2023).

What are the patient characteristics, co-morbidities, and are they able to use the device easily?

Considering the complete profile and co-morbidities of a patient is important in selecting a device; assessing their ability to properly use a device is also important. Although migraine is one of the most common neurological diseases that more predominantly affects women starting at around age 14 and peaking at approximately 30 years of age, the clinical epidemiological data with respect to race and ethnicity has not been clearly elucidated.[148] The demographic and baseline characteristics in all of the adult clinical trials reviewed above reflect the known epidemiological characteristics of patients with migraine, predominantly female with participant mean ages falling between 30-40 years of age. The US-based studies had a higher proportion of Caucasian participants. Interestingly, the highest age-standardized prevalence rates for migraine are found in Belgium and:[148] Belgium is where the first noninvasive neuromodulation clinical studies were completed (Cefaly, whose parent company is based in Belgium). The highly robust PRESTO investigation of nVNS (gammacore) took place in Italy.

Devices like the cervical nVNS have far broader evidenced-based approved applications beyond migraine in both Europe and the US.[149] For mood disorders, cervical nVNS is used to treat PTSD in US Veterans. GammaCore achieved FDA breakthrough designation[150] in 2022 for all patients with PTSD based on a study that demonstrated meaningful reduction of PTSD symptoms.[151] Like invasive vagal nerve stimulation for

depression, nVNS is an emerging potential treatment for depression[152] and the gammaCore device is CE marked for treating depression in Europe.

The principal of CSD is notable for patients with a history of traumatic brain injury (TBI) as CSD can be a sequelae of TBI. Complex headaches including migraine are one of the most common outcomes of TBI; a device such as sTMS or nVNS may be the best choice in this clinical scenario or even combining sTMS with nVNS.[153] For those with skin sensitivity, sTMS may be a better choice as there is no risk of skin irritation from direct electrode contact or electrical current.

As highlighted under the Relivion discussion, cephalic neuralgias send afferent signals through the same migraine-pain pathways. Peripheral nerve stimulation research and clinical application in the treatment of cephalic neuralgias and secondary headaches evolved first from invasive modalities such as implanted occipital stimulation (for occipital neuralgia and cervicogenic headache) and trigeminal (for trigeminal neuralgia) to investigating these same stimuli locations (first invasive then transcutaneous) for treating primary headaches such as migraine. These neuralgias can serve as somatic triggers for migraine. In patients with these co-morbidities, adjunct treatment with noninvasive neuromodulation makes good clinical and practical sense.

The most important question is which device lends itself to the greatest compliance and is easiest for the patient to use. Most of the devices are small and fairly portable but for the sTMS eNeura device. Though intended to be portable, the SAVI Dual weighs around 3 lbs and is the most expensive device. Some of the devices require regular replacement of the device itself (REN) or consumables (such as gel for nVNS or adhesive pads for Cefaly). And importantly, there is managing the technology itself (being able to turn it on, use it correctly), whether a "smart phone" is needed for a Bluetooth enabled device, being able to use an associated application, etc. The smartphone-controlled features of Nerivio may enhance user engagement and adherence in younger populations. Having demo units on hand for patients to experience and test out their preference is strongly recommended[154] as well as consulting the manufacturers' complete instructions on indications and contraindications.

What is the safety profile and contraindications?

The safety profile for all of the devices rises above prescription migraine medications and does not carry the risk of medication overuse headaches. Currently, all devices share the contraindication in persons with metal implants in close proximity to the treatment area or active implanted electrical devices such as a pacemaker or hearing aid, with some important exceptions such as Inspire (for sleep apnea) in the case of nVNS. As long as the Inspire device is off, nVNS is allowed. There are clinical studies underway that are examining concomitant use of noninvasive neuromodulation devices in persons with implantable devices, as well as in patients with other conditions such as opioid use disorder, post-stroke recovery, Parkinson's, etc.[155]

Returning to our key demographic, women of childbearing years, the AHS 2021 guidelines point out that there has been no reports of fetal malformations or birth defects observed in animal studies, post-marketing surveillance, or open-label studies for sTMS or nVNS. After these guidelines were published, a retrospective study[112] of the safety of REN in pregnant women treated during pregnancy (n=59) vs controls (n=81) and looking at data 3 months postpartum indicated the device was safe, finding no significant differences between the two groups and examined outcomes (gestational age at delivery, newborn weight, miscarriage rate, preterm birth rate, birth defect rate, stillbirth rate, rate of newborns meeting developmental milestones at 3 months postnatal and emergency room visits). The 2023 American College of Obstetricians and Gynecologists (ACOG) guidelines[156] and as reiterated in Practical Neurology regarding management of

migraines in pregnant and postpartum women, briefly point to noninvasive neuromodulation (specifically GammaCore, CEFALY, Nerivio, and sTMS) as options for the treatment and prevention of migraines with the added caution that there is limited safety data for these options.[3]

Conclusion

The American Headache Society (AHS) Consensus Statement and Update Integrating New migraine Treatments into Clinical Practice[157] recommends the use of neuromodulation *including as first line treatment* under several circumstances. This also brings us squarely back to the largest key demographic affected by migraine, women of childbearing years particularly those who are pregnant, lactating, or planning for pregnancy. In thinking about all adult populations, important specifics of the AHS recommendations regarding neuromodulation include:

- A trial of neuromodulation where triptans are contraindicated.
- Using neuromodulation for those who prefer non-drug treatments.
- To defer to neuromodulation when migraine pharmacotherapy has been inadequate or there is poor tolerability to migraine medications.
- Using neuromodulation in those at risk for developing medication overuse headache (as an adjunct).
- "For preventive treatment, *all (emphasis added)* patients should be considered for a trial of a neuromodulatory device as an adjunct to the existing treatment plan."

Moreover, according to the AHS consensus statement the shared goals of acute and preventative treatment of migraine should include:

- Effective treatments that are safe and reliable
- Promote self-care
- Reduce healthcare utilization
- Address the full spectrum of symptoms
- Reduce disability, improve function, and increase quality of life in a cost effective manner

Collectively through clinical trials, post-hoc analysis, and post-marketing data we have seen that several noninvasive neuromodulation modalities not only have proven to be safe and effective, but also have the potential to achieve all of these recommended goals.

The current major barrier in the US is lack of coverage of these devices by health insurance, including government programs. The exception being the US Veterans Administration, which covers all of the devices discussed above. In the US out of pocket costs for migraine medications for non-veterans can range from $550 to greater than $1500/month even for those who receive government healthcare such as Medicaid recipients.[158] Compared to the out of pocket costs of these devices ($400-600/month) there may be both savings and additional benefits.

The safety profile of noninvasive neuromodulation cannot be overstated and the avoidance of pharmaceutical risks, medication overuse headaches, and adverse events particularly in women, pediatrics, and adolescents and by extrapolation in older adults who tend to have higher cardiovascular risk profiles compared to younger adults. There are few device contraindications: Notable are implanted metal and active electrical devices common to all and even the latter is currently being explored. Noninvasive neuromodulation can be used as monotherapy or in conjunction with other treatments for additive benefit

as recommended by AHS. Considering all factors, moving noninvasive neuromodulation to first line treatment as monotherapy or adjunctive therapy for all patients is reasonably warranted.

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Device Images*

nVNS

eTNS

eC-TONS

REN

sTMS

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Comparison Tables

Device Type	*nVNS*	*eTNS*	*eC-TONS*	*REN*	*sTMS*
Device Commercial Name	gammaCore	Cefaly	Relivion	Nerivio	SAVI Dual or sTMS Mini (eNeura)
Stimulation type	Transcutaneous Electrical	Transcutaneous Electrical	Transcutaneous Electrical	Transcutaneous Electrical	Electromagnetic
Indication	Migraine with and without aura: **Acute and Prevention**	Migraine with and without aura: **Acute and Prevention**	Migraine with and without aura: **ACUTE ONLY**	Migraine with and without aura: **Acute and Prevention**	Migraine with and without aura: **Acute and Prevention**
FDA Approved/CE Mark for migraine	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes	Yes/Yes
Other Clinical Applications?	Yes: 6 headache indications including Cluster HA, Hemcrania; PTSD (Veterns); IBS (CE only)	No	No	No	No
Stimulation parameters	Max 60 mA. Peak voltage of 24-V.. Frequency is a proprietary 5 Mhz sine wave burst repeated every 40 ms (25 Hz).	Max 16 mA. Maximum skin impedance of 2.2 kOhms. Rectangular biphasic symmetrical pulses of 250 µs with zero electrical mean. Acute treatment frequency 100 hz. Prevention frequency 60 hz.	Max amplitudes are for frontal 6mA and occipital 12mA. Symmetrical biphasic waveforms with phase duration of 330– 400 ms. Frequency 80 hz with a phase rise 5 µS.	Max 40 mA. Patented biphasic rectangular waveform delivered via a single channel at a modulated frequency between 100Hz and 120H with a 400µs pulse width.	0.9 Tesla
Target Pathway	***Peripheral:*** Vagal nerve pathway in the neck	***Peripheral:*** Supraorbital and supratrochlear branches of the trigeminal ophthalmic division (V1)	***Peripheral:*** Combined supraorbital and supratrochlear V1 pathway and greater occipital nerve branches	***Peripheral:*** Nociceptive Aδ and C-fibers (Conditione Pain Modulation)	***Cortical:*** Bilateral occipital lobes (to disrupt CSD)
Pediatric or Adolescent Use	Adolescent (12 and older)	Not approved	Not approved	Adolescent and Pediatric (8 and older)	Adolescent (12 and older)
Treatment Time *Abort (PRN)*	4 min total/treatment	60-120 min total/treatment	60 min total/treatment	45 min/treatment	@10 min total (4 sequential pulses)
Treatment Time *Prevent*	4 min total TID	20 min daily	N/A	45 min every other day	@10 min total BID (4 sequential pulses)

Device Type	*nVNS*	*eTNS*	*eC-TONS*	*REN*	*sTMS*
Side Effects *(Transient and resolve)*	• Site/skin irritation or erythema • Nasopharyngitis • Facial tingling or spasm	• Site/skin irritation or paresthesia • Tingly sensation after treatment • Headache/migraine • Sedation during and after treatment.	• Site/skin irritation or paresthesia • Tingly sensation after treatment • Headache/migraine • Sedation during and after treatment • Nausea • Dizziness during or after treatment	• Redness and/or irritation at the application site • A sensation of warmth or tingling at the application site • Arm numbness or muscle spasm where the device is applied	• Lightheadedness • Cranial tingling • Tinnitus
Contraindications *(Consult the manufacture's guidelines for complete list and updates.)*	Active implantable electronic devices, implanted or metallic devices at or near the neck. Cannot be used if using another device simultaneously (i.e. Inspire). **Cautions:** Has not been evaluated in patients with carotid or other atherosclerotic disease, cervical vagotomy, clinically significant hypertension, hypotension, bradycardia, tachycardia, seizure disorder, prolonged QT, cardiac arrhythmia, abnormal baseline EKG, abnormal cervical anatomy or brain tumor.	Active implantable electronis devices, implanted or metallic devices in the face or head, recent facial or brain trauma (within 3 months), pain of unknown origin, trigeminal neuralgia, opthalmic shingles. Not be used within 48-72 hours of onabotulinumtoxinA injections.	Active implantable electronic devices, implanted or metallic devices in the face, head or neck, recent facial or brain trauma (within 3 months). Not be used within 72 hours of onabotulinumtoxinA injections.	Active implantable electronic devices, cannot be used in an arm with implanted or metallic devices, uncontrolled epilepsy. **Cautions**: Has not been evaluated in patients with congestive heart failure, severe cardiac or cerebrovascular conditions.	Active implantable electronic devices or metal or conductive materials in head, neck or upper body, history of stroke brain aneurysm/clips/coil, cochlear implants, cerebrospinal fluid shunts, metal implants in the skull, neck, shoulder, arm or hands, metallic heart valves, radioactive seeds or facial tattoos with metallic ink. **Cautions:** Has not been evaluated in patients with congestive heart failure, severe cardiac or cerebrovascular conditions. (Dental implants, fillings or other dental appliances are okay and are not affected by the device.)
Prescription needed?	Yes	**No**	Yes	Yes	Yes
Prescriber training/support	Yes	Yes	Yes	Yes	Yes
Patient Coaching/Assistance	Yes	Yes	Yes	Yes	Yes
Smartphone required?	No	Optional	Optional	Yes	No
Consumables	Contact gel	Adhesive pad, replacement depends on usage.	Electrode pad set (6).	The device itself, allows for 18 total 45 mins sessions.	None
Cost to patient if not covered. *(Prices continue to go down or additional flex plans are added with increased market sales for most devices.)*	Variable and potentially negotiable. Device is usually loaded with 3 months of treatment and can be "refilled" with a digital card. Pricing not listed on website, but for 31 days of treatment can be up to $625/month and as low as $200/month. Discount programs can reduce cost to just over $50 for the device and 31 days of treatment	One-time device purcahse varies from $330 to $500; 3 electrode packages cost $25, ordered every 2-3 months; 90-day return policy.	A $150 one-time cost for the first 60 days of use, if patient wishes to continue several options to purchase the device for as low as $650.	$49 for 1 device (18 treatments), $89/ device thereafter, $66/device if 3 are bought ($199 total).	A $1050 one-time cost for 3 months, then $399/month to rent; the prescription must be sent to a specialized pharmacy as the device is not considered Durable Medical Equipment in the US, but as a pharmaceutical.

Device Type	*nVNS*	*eTNS*	*eC-TONS*	*REN*	*sTMS*
ACUTE **Key Clinical Evidence:** *IHS Clincial Trial Criteria followed or included (to some degree)*	Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized **PRESTO** study. (2018)	Phase 3 randomized, double-blind, sham-controlled Trial of e-TNS for the Acute treatment of Migraine. (**TEAM**) (2022)	Migraine treatment with external concurrent occipital and trigeminal neurostimulation-A randomized controlled trial. **(RIME)** (2022)	Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. (2019)	Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomized, double-blind, parallel-group, sham-controlled trial. (2010)
PREVENT **Key Clinical Evidence:** *IHS Clincial Trial Criteria followed or included to some degree.*	• Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The **EVENT** study (2016). • Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomized, sham- controlled **PREMIUM** trial (2019). • Non-invasive vagus nerve stimulation for prevention of migraine: The multicenter, randomized, double-blind, sham-controlled **PREMIUM II** trial (2022).	**PREMICE**. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. (2013)	Not yet.	Remote electrical neuromodulation for migraine prevention: A double-blind, randomized, placebo-controlled clinical trial. (2023)	Not an RCT.
Evidence for Most Bothersome Symptom Efficacy (N/V, Photophobia or Phonophobia)	No	Yes	Yes	Yes (Adults) ? (Adolescents) Yes (Pediatrics)	No
Additional Clinical Evidence	• Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: additional findings from the randomized, sham-controlled, double-blind **PRESTO** trial (2018) • Practical and clinical utility of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: a post hoc analysis of the randomized, sham-controlled, double-blind **PRESTO** trial (2018).	Acute migraine therapy with external trigeminal neurostimulation (**ACME**): A randomized, controlled trial. (2019)	Not yet.	Thus far, 21 peer-reviwed publications of Real World Evidence (RWE) and Open Label for a total of 15,000 patients substantiating safety and supporting efficacy. (See Table)	A Multicenter, Prospective, Single Arm, Open Label, Post-Market, Observational Study to evaluate the use of sTMS in reduction of Migraine Headache. (**ESPOUSE Study**) (2018) *Post-Market for difficult to treat migraine and medication overuse headache.*
Mechanism of Action Verified	Yes	No	*Preclinical Invasive Data*	No (Pending)	Yes

Device Type	nVNS	eTNS	eC-TONS	REN	sTMS
Pediatric Adolescent Evidence	Non-invasive vagus nerve stimulation (nVNS) as symptomatic treatment of migraine in young patients: a preliminary safety study (2017). *Small (N=9) Open-label feasibiilty, safety, and efficay trial*	Pending (Clinical Trial)	No	● **ADOLESCENT:** Remote electrical neuromodulation for acute treatment of migraine in adolescents. (2021) >>> ***Open label,*** *45 participants performed at least 1 treatment to abort for analysis.* ● **PEDIATRIC:** Acute treatment of migraine in children aged 6–11: Real-world analysis of remote electrical neuromodulation. (2024) >>> *Open label, RWE analysis of children ages 6-11 (N=293, MEDIAN age 11, IQR 9-11, 73% girls) who were prescribed Nerivio off-label.*	Transcranial Magnetic Stimulation for Migraine Prevention in Adolescents: A Pilot Open-Label Study. Headache. (2018) *Small (N=12) feasibiilty, safety, and efficay trial*
Safe in pregnancy	> No clinical trials > No post-marketing adverse events reported	> No clinical trials > No post-marketing adverse events reported	> No clinical trials > No post-marketing adverse events reported	> No clinical trials > No post-marketing adverse events reported > Retrospective controlled survey-study.	> No clinical trials > No post-marketing adverse events reported > Post marketing survey of three (3) pregnant women, no adverse events reported.
Published Safety Evidence in Pregnancy	No	Pending (Register)	No	Safety of remote electrical neuromodulation for acute migraine treatment in pregnant women: A retrospective controlled survey-study. (2023) REN (59), Controls (81) No differences in several pregnancy, birth, or infant outcomes.*	Single pulse transcranial magnetic stimulation (sTMS) as a non-drug treatment option for pregnant patients with migraine. Abstract. International Headache Congress. (2013)

*Gestational age at delivery, newborn weight, miscarriage rate, preterm birth rate, birth defect rate, stillbirth rate, rate of newborns meeting developmental milestones at 3 months postnatal and emergency room visits.

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[33] The term "TENS" is used here to describe any device which transmits a current transcutaneously. TENS in the US has been misunderstood as applying only to a certain range of stimulus and only for localized pain treatment. In the US, the misunderstanding arose from previous commercial TENS devices with a limited stimulus parameter being used for and billed under a particular coding scheme for principally localized muscular-skeletal pain. The presumption regarding these devices was that there was no central effect, such as global endogenous opioid release, from a sub-pain stimulus. The FDA and Centers for Medicare and Medicaid (CMS) in an effort to distinguish devices such as Nerivio in terms of mechanism and for coding and billing purposes created a distinct category - REN - for the Nerivio. The FDA has qualified Nerivio as a "Distal Transcutaneous Electrical Stimulator For Treatment Of Acute Migraine, trunk and limb electrical stimulator to treat headache." Only acute migraine is included in this definition currently. CMS uses the definition "Distal transcutaneous electrical nerve stimulator, stimulates peripheral nerves of the upper arm" with HCPCS code of A4540. It does specify treatment target.

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[40] In the author's clinical experience, the abortive treatment protocol can be shortened to delivering 4 min treatment cycles every 15 mins with improved effect and no adverse effects. The fifteen min interval is based on the PRESTO clinical study. Also, using the device with the onset of prodromal symptoms and onset of aura to abort migraine is clinically feasible but not yet validated in a clinical trial. Real world evidence is demonstrating this is clinically effective, but not yet published.

[41] Studies included patients stable on both oral abortive and preventative medications but excluded any receiving nerve blocks or chemo-denervation within a certain period to account for any confounding effects. However, in the clinical setting, these interventions are not contraindicated.

[42] Electrocore, the manufacturer of gammaCore, has a twin non-prescription device called Truvaga not sold for migraine but for stress reduction and only available in the US. This updated device is bluetooth-enabled through an application including a stress/symptom and treatment "diary" function.

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[47] Of note, the PRESTO study only used ITT analysis and did not employ a modified ITT analysis or per protocol analysis as allowed by IHS criteria that would have potentially accounted for protocol deviations and effect on the final outcomes. This is important in that the protocol instructed participants to treat within 20 mins of pain onset. But there was no data set for when treatment was initiated. The study did document that more participants in the treatment group tended to wait until their pain was severe to treat, however this was not statistically different from the sham group. There was consideration as to whether this delay affected the primary endpoint not being statistically significant. The ad-hoc repeat measures analysis did show superiority at 120 mins. What cannot be determined is if this tendency of the active groups to wait until the pain was severe also included waiting greater than 20 mins to treat and hence also impacted the primary outcome.

[48] The one quality systematic review and meta-analysis of noninvasive vagal nerve stimulation for migraine (Song D, 2023) grouped both cervical and auricular modalities in the analysis. However, four of the six studies were of the gammaCore device, and the two auricular studies included were of low quality using different experimental devices. This publication's findings are not included in this chapter. and neither a review of auricular vagal nerve stimulation devices. None of the auricular devices on the market is by prescription, nor has been (like Cefaly). There is a lack of clinical evidence regarding the safety and efficacy of these devices.

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[70] The ACME treatment time period of 1hr coincides with the primary outcome, pain score change measured at 1 hr. This is similar to the TEAM study of 2022 that had a 2 hr treatment protocol and a 2 hr primary outcome measure of pain-freedom. The TEAM study with the longer treatment period of 2 hrs demonstrated both sustained pain relief and reduction that was statistically different at 2 hrs and 24hrs. The ACME study demonstrated statistically significant sustained pain reduction at 1, 2 and 24 hrs, but not pain-freedom (only at the 1hr measuring point). These studies taken together indicate that a longer treatment session is needed 2 hrs- and as the authors of the ACME study speculated. However, the device currently is set for and FDA approved to deliver a 60-min session. It can be reinitiated for another 60 min session, as there is no limit to do so.

[71] Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, Magis D. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology. 2013 Feb 19;80(8):697-704. doi: 10.1212/WNL.0b013e3182825055. Epub 2013 Feb 6. PMID: 23390177. (PREMICE).

[72] Jiang L, Yuan DL, Li M, Liu C, Liu Q, Zhang Y, Tan G. Combination of flunarizine and transcutaneous supraorbital neurostimulation improves migraine prophylaxis. Acta Neurol Scand. 2019 Mar;139(3):276-283. doi: 10.1111/ane.13050. Epub 2018 Dec 11. PMID: 30428122.

[73] Yushuang Deng, Min Zheng, Lanying He, Juan Yang, Gang Yu, Jian Wang. A Head-to-Head Comparison of Percutaneous Mastoid Electrical Stimulator and Supraorbital Transcutaneous Stimulator in the Prevention of Migraine: A Prospective, Randomized Controlled Study. Neuromodulation: Technology at the Neural Interface. 2020;23(6):770-777. doi: 10.1111/ner.13127.

[74] The latter two trials - Jiang et al, 2019 and Deng et al, 2020 - did not specifically look at Cefaly vs sham but at: eTNS alone vs flurnarizine vs eTNS+flurnarizine; and eTNS vs percutaneous mastoid electrical stimulation, respectively. These trials are not reviewed here but they indicate both eTNS and mastoid electrical stimulation demonstrated efficacy in treating migraine.

[75] Schoenen J. Addendum to “Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial” [electronic response to Schoenen et al., Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial]. Neurology. 2015. Available at: http://www.neurology.org/content/80/8/697/reply#neurology_el;64113.

[76] Gérardy P, Fabry D, Fumal A, Schoenen J. A pilot study on supra-orbital surface electrotherapy in migraine. Cephalalgia. 2009;29:134.

[77] Magis D, Sava S, d'Elia TS, Baschi R, Schoenen J. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain. 2013 Dec 1;14(1):95. doi: 10.1186/1129-2377-14-95. PMID: 24289825; PMCID: PMC4177534

[78] Riederer F, Penning S, Schoenen J. Transcutaneous Supraorbital Nerve Stimulation (t-SNS) with the Cefaly® Device for Migraine Prevention: A Review of the Available Data. Pain Ther. 2015 Oct 14;4(2):135–47. doi: 10.1007/s40122-015-0039-5. Epub ahead of print. PMID: 26467451; PMCID: PMC4676766.

[79] Vikelis M, Dermitzakis EV, Spingos KC, Vasiliadis GG, Vlachos GS, Kararizou E. Clinical experience with transcutaneous supraorbital nerve stimulation in patients with refractory migraine or with migraine and intolerance to topiramate: a prospective exploratory clinical study. BMC Neurol. 2017 May 18;17(1):97. doi: 10.1186/s12883-017-0869-3. PMID: 28521762; PMCID: PMC5437420.

[80] Magis D, D'Ostilio K, Thibaut A, et al. Cerebral metabolism before and after external trigeminal nerve stimulation in episodic migraine. Cephalalgia. 2017;37(9):881-891. doi:10.1177/0333102416656118

[81] Russo A, Tessitore A, Esposito F, Di Nardo F, Silvestro M, Trojsi F, De Micco R, Marcuccio L, Schoenen J, Tedeschi G. Functional Changes of the Perigenual Part of the Anterior Cingulate Cortex after External Trigeminal Neurostimulation in Migraine Patients. Front Neurol. 2017 Jun 15;8:282. doi: 10.3389/fneur.2017.00282. PMID: 28663737; PMCID: PMC5471296.

[82] M Piquet et al. Supraorbital transcutaneous neurostimulation has sedative effects in healthy subjects. BMC Neurol. 2011;11:135. doi: 10.1186/1471-2377-11-135.

[83] Reed K, Black S, Banta C, Will K. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: Initial experience. Cephalalgia. 2010;30(3):260-271. doi:10.1111/j.1468-2982.2009.01996.x.

[84] Johnson M. Transcutaneous Electrical Nerve Stimulation: Mechanisms, Clinical Application and Evidence. Rev Pain. 2007 Aug;1(1):7-11. doi: 10.1177/204946370700100103. PMID: 26526976; PMCID: PMC4589923.

[85] Lauritsen CG, Silberstein SD. Rationale for electrical parameter determination in external trigeminal nerve stimulation (eTNS) for migraine: A narrative review. Cephalalgia. 2019;39(6):750-760. doi:10.1177/0333102418796781.

[86] In addition to the pre-clinical studies and RCT on the efficacy and safety of this specific device, in achieving FDA approval Relivion also included Cefaly as the proposed predicate device, hence associating Cefaly's safety and efficacy data.

[87] The Relivion parent company is Neuolief, not to be confused with Neuralieve the original parent company of the sTMS device(s) discussed in this chapter that is now manufactured by eNeura.

[88] This is the pivotal research that leads from invasive to transcutaneous modalities for migraine and the design of eC-TONS (Relivion). Reed K, Black S, Banta C, Will K. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: Initial experience. Cephalalgia. 2010;30(3):260-271. doi: 10.1111/j.1468-2982.2009.01996.x. (First published in 2009).

[89] Peripheral nerve stimulation research and clinical application in the treatment of cephalic neuralgias and secondary headaches evolved first from invasive modalities such as implanted occipital stimulation (for occipital neuralgia and cervicogenic headache) and trigeminal (for trigeminal neuralgia) to investigating these same stimuli locations, first invasive then transcutaneous, for treating primary headaches such as migraine. Cephalic neuralgias can serve not only as somatic triggers for migraine but send afferent signals through the same migraine-pain pathways, hence, the pragmatic investigational progression to clinical application.

[90] There is mention in a short article of a prevention RWE pilot (N=17) indicating potential efficacy, but there is no peer-reviewed data, thus far. Sharon R, Daniel O, Tepper SJ. Efficacy of Relivion® MG in the Acute and Preventive Treatment of Migraine. Findings from Two Recent Studies. (P7-2.002). Neurology. 2022 May;98(18_supplement). doi: 10.1212/WNL.98.18_supplement.1640.

[91] Daniel O, Sharon R, Tepper SJ. A device review of Relivion®: an external combined occipital and trigeminal neurostimulation (eCOT-NS) system for self-administered treatment of migraine and major depressive disorder. Expert Rev Med Devices. 2021;18(4):333-342. doi: 10.1080/17434440.2021.1908122.

[92] Application assumes consent to data sharing of Personal Health Information and de-identified data, unlike Nerivio where the user must read and consent before completing the application account. The Relivion Privacy Policy and End User Agreement are accessible through the application, but it is assumed that the user has read these. Both these documents are very broad and cover use of the website and application as well as miscellaneous topics not specific to device or application use. The user agreement entangles terms regarding both the patient and prescriber. Per the website, the platform for patient data collection and sharing is AI enhanced but does not specify how. There is no mention in the agreements regarding AI and consent to AI.

[93] https://www.relivion.com/faq/. The user manual and website also state that for acute treatment, a minimum of 8-12 weeks is needed to see results. However, the basis for this statement is uncertain as there is no data or studies to support this and the clinical trials demonstrated immediate effect.

[94] For the occipital electrodes there are water-releasing covers to help provide proper electrical conductivity between the electrodes and the scalp.

[95] Tepper SJ, Grosberg B, Daniel O, Kuruvilla DE, Vainstein G, Deutsch L, Sharon R. Migraine treatment with external concurrent occipital and trigeminal neurostimulation-A randomized controlled trial. Headache. 2022 Sep;62(8):989-1001. doi: 10.1111/head.14350. Epub 2022 Jun 24. PMID: 35748757. (RIME)

[96] The initial device malfunction affected the first 50 cases. Because the malfunction resulted in failure to deliver stimulation, these participants were not analyzed for efficacy but were analyzed for safety, and the results were consistent with those reported for the ITT population.

[97] Not defined in the study publication or the users manual.

[98] The published study states that on the mITT population a per-protocol analysis was conducted as well for all participants who had no major protocol deviations, but there is no distinct data presented for this analysis.

[99] Clinically meaningful relief of co-morbid most bothersome symptoms has been found in pediatric patients with Nerivio. See section on Nerivio.

[100] A summary and the data analysis from these trials was included in the FDA application. One of the trials was presented at the International Headache Society meeting in 2017 by Hering-Hanit. It was a prospective, randomized, double-blind, parallel-group, sham-controlled investigation (N=33) conducted at the Meir Medical Center, Israel in 2014-2015. It found statistically significant pain relief (time point not specified) and freedom (2 and 24 hrs) as well as improved function. Adverse events were not discussed. The second trial included in the FDA application was the SP-301 study, a prospective, randomized, double-blind, parallel-group, sham-controlled investigation (N=55) conducted at the Laniado Medical Center in Israel in 2018. Statistically significant pain relief at one and two hrs was found as well as higher responder rate in the treatment group with no serious adverse events. Hering-Hanit R. A prospective, randomized, single blind, parallel-group, placebo controlled clinical study to evaluate the short-term effectiveness of combined occipital and supraorbital transcutaneous nerve stimulation (OS-TNS) in treating migraine. International Headache Society meeting in 2017, Cephalalgia. 2017;37(1_suppl):52-171.

[101] Headache and Facial Pain Unit, Laniado Medical Center; Netanya, Israel.

[102] Daniel O, Tepper SJ, Deutsch L, Sharon R. External Concurrent Occipital and Trigeminal Neurostimulation Relieves Migraine Headache: A Prospective, Randomized, Double-Blind, Sham-Controlled Trial. Pain Ther. 2022 Sep;11(3):907-922. doi: 10.1007/s40122-022-00394-w. Epub 2022 Jun 4. PMID: 35661128; PMCID: PMC9314547. (RIME study).

[103] "These clinical results were substantially higher in aborting migraine compared to a 60 min session of single-channel non-invasive trigeminal neurostimulation. In that [ACME] study, treated subjects achieved a net response rate of 29%, 18%, and 17% at 1, 2, and 24 h, respectively, compared to a net response of 42.8%, 34.7%, and 37% in the present study with eCOT-NS."

[104] Rapoport AM, Lin T, Tepper SJ. Remote electrical neuromodulation (REN) for the acute treatment of migraine. Headache. 2020;60(1):229-234.

[105] https://nerivio.com/how-it-works/ (https://nerivio.com/how-it-works/). Accessed Dec 05, 2024

[106] There are plans to investigate the proposed mechanism of action per David Yarnitsky, MD, Director and Professor of the Department of Neurology at the Rambam Health Care Campus Haifa, and Medical Advisor for Theranica the manufacturer of Nerivio (December 17, 2024).

[107] As part of the sign-up process for the Nerivio application, all users must accept terms of use of which includes that their de-identified data may be used for research purposes. Per Nerivio, users are not obligated to provide personal information and can treat without providing feedback. However, when creating an account, how to reject the data sharing consent is not clearly apparent.

[108] Yarnitsky D, Volokh L, Ironi A, Weller B, Shor M, Shifrin A, Granovsky Y. Nonpainful remote electrical stimulation alleviates episodic migraine pain. Neurology. 2017 Mar 28;88(13):1250-1255. doi: 10.1212/WNL.0000000000003760. Epub 2017 Mar 1. PMID: 28251920.

[109] Yarnitsky D, Dodick DW, Grosberg BM, Burstein R, Ironi A, Harris D, Lin T, Silberstein SD. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial. Headache. 2019 Sep;59(8):1240-1252. doi: 10.1111/head.13551. Epub 2019 May 9. PMID: 31074005; PMCID: PMC6767146.

[110] OnabotulinumtoxinA, nerve blocks or preventative IV infusions can be used concurrently with clinical use.

[111] Tepper SJ, Rabany L, Cowan RP, Smith TR, Grosberg BM, Torphy BD, Harris D, Vizel M, Ironi A, Stark-Inbar A, Blumenfeld AM. Remote electrical neuromodulation for migraine prevention: A double-blind, randomized, placebo-controlled clinical trial. Headache. 2023 Mar;63(3):377-389. doi: 10.1111/head.14469. Epub 2023 Jan 27. PMID: 36704988.

[112] Peretz A, Stark-Inbar A, Harris D, Tamir S, Shmuely S, Ironi A, Halpern A, Chuang L, Riggins N. Safety of remote electrical neuromodulation for acute migraine treatment in pregnant women: A retrospective controlled survey-study. Headache. 2023 Jul-Aug;63(7):968-970. doi: 10.1111/head.14586. Epub 2023 Jun 19. PMID: 37335242.

[113] Grosberg B, Rabany L, Lin T, Harris D, Vizel M, Ironi A, O'Carroll CP, Schim J. Safety and efficacy of remote electrical neuromodulation for the acute treatment of chronic migraine: an open-label study. Pain

Rep. 2021 Oct 14;6(4):e966. doi: 10.1097/PR9.0000000000000966. PMID: 34667919; PMCID: PMC8519197.

[114] Synowiec A, Stark-Inbar A, Weinstein M, et al. One-Year Consistent Safety, Utilization, and Efficacy Assessment of Remote Electrical Neuromodulation (REN) for Migraine Treatment. Adv Ther. 2024;41:170-181. doi: 10.1007/s12325-023-02697-6.

[115] Nierenburg H, Vieira JR, Lev N, Lin T, Harris D, Vizel M, Ironi A, Lewis B, Wright P. Remote Electrical Neuromodulation for the Acute Treatment of Migraine in Patients with Chronic Migraine: An Open-Label Pilot Study. Pain Ther. 2020 Dec;9(2):531-543. doi: 10.1007/s40122-020-00185-1. Epub 2020 Jul 9. PMID: 32648205; PMCID: PMC7648773.

[116] Grosberg B, Rabany L, Lin T, Harris D, Vizel M, Ironi A, O'Carroll CP, Schim J. Safety and efficacy of remote electrical neuromodulation for the acute treatment of chronic migraine: an open-label study. Pain Rep. 2021 Oct 14;6(4):e966. doi: 10.1097/PR9.0000000000000966. PMID: 34667919; PMCID: PMC8519197.

[117] Hershey AD, Lin T, Gruper Y, Harris D, Ironi A, Berk T, Szperka CL, Berenson F. Remote electrical neuromodulation for acute treatment of migraine in adolescents. Headache. 2021 Feb;61(2):310-317. doi: 10.1111/head.14042. Epub 2020 Dec 21. PMID: 33349920.

[118] Werener K, et al. Acute treatment of migraine in children aged 6−11: Real-world analysis of remote electrical neuromodulation (REN). Ann Child Neurol Soc. 2024. doi: 10.1002/cns3.20073.

[119] The SAVI Dual device has undergone several name changes including Spring TMS and then sTMS Mini but not treatment parameters. eNeura (then called Neuralieve) went out of business in 2019, and reentered the market with the SAVI Dual in the US. The sTMS Mini under eNeura is still approved and marketed in the UK and Australia for both acute and preventative treatment in adults. In the UK and Australia the sTMS Mini is used and not the SAVI Dual because the SAVI Dual requires a cellular network for renewal of prescriptions and the device is not compatible with networks in the UK or Australia. The sTMS Mini uses a SIM card instead. The SAVI Dual is undergoing reconfiguring to be compatible with other cellular networks. Otherwise, the SAVI Dual and sTMS Mini are identical in terms of treatment parameters. The SAVI Dual has been validated until 2028 to meet CE mark requirements and is pending re-entry into the European market per communications with eNeura's sales VP, Eric Bohlen (12/28/2024).

[120] Lipton RB, Pearlman SH. Transcranial magnetic stimulation in the treatment of migraine. Neurotherapeutics. 2010 Apr;7(2):204-12. doi: 10.1016/j.nurt.2010.03.002. PMID: 20430320; PMCID: PMC5084102. Available at: https://doi.org/10.1016/j.nurt.2010.03.002.

[121] Jolij J, Lamme VA. Transcranial magnetic stimulation-induced 'visual echoes' are generated in early visual cortex. Neurosci Lett. 2010 Nov 5;484(3):178-81. doi: 10.1016/j.neulet.2010.08.045. Epub 2010 Aug 21. PMID: 20732388.

[122] Holland PR, et al. Transcranial magnetic stimulation for the treatment of migraine aura? Cephalalgia. 2009;29(Supplement 1):22-22.

[123] The patient instruction manual uses the phrase "the earliest indication of an attack" (p.11). SAVI Dual Migraine Therapy Instructions for Use Patient Manual. Available at: https://www.eneura.com/wp-content/uploads/2023/06/SAVI-Dual-Patient-Instructions-for-Use-LBL-0188-Rev-N.pdf.

[124] SAVI Dual Migraine Therapy Instructions for Use Patient Manual. (p.11). The original protocol was 3 pulses with 15 mins in between, then 4 pulses with 15 mins in between. The current clinical protocol is 4 pulses, with a "brief pause" that is not time de-limited.

[125] Though not yet clinically validated, those with clear prodromal symptoms may use the device to head off a migraine attack and is recommended by eNeura staff clinicians, hence "the earliest indication of an attack", per communications with eNeura's sales VP, Eric Bohlen (12/28/2024). This would make sense when considering brain hyperexcitability is the precursor to CSD, the therapeutic target of sTMS. In the author's clinical experience treating known prodrome symptoms has aborted migraine attacks.

[126] Communications with eNeura's sales VP, Eric Bohlen (12/28/2024).

[127] Clarke BM, Upton AR, Kamath MV, Al-Harbi T, Castellanos CM. Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain. 2006 Oct;7(5):341-6. doi: 10.1007/s10194-006-0329-8. Epub 2006 Oct 25. PMID: 17058041; PMCID: PMC3468174.

[128] Mohammad YM, Kothari R, Hughes G, Krumah MN, Fischell S, Fischell R, et al. Transcranial magnetic stimulation (TMS) relieves migraine headache. Headache. 2006;46:839.

[129] Mohammad YM, Hughes G, Krumah MN, Fischell S, Fischell R, Ruppel R, Schweiger J. Self-administered transcranial magnetic stimulation (TMS) during the aura phase improves and aborts migraine headache. Eur J Neurol. 2006 Sep;13:247.

[130] By Neuralieve the precursor name of eNeura.

[131] Data is from only 16 centers as two centers did not enroll participants after screening.

[132] Lipton RB, Dodick DW, Silberstein SD, Saper JR, Aurora SK, Pearlman SH, Fischell RE, Ruppel PL, Goadsby PJ. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol. 2010 Apr;9(4):373-80. doi: 10.1016/S1474-4422(10)70054-5. Epub 2010 Mar 4. PMID: 20206581.

[133] Dodick DW, Schembri CT, Helmuth M, Aurora SK. Transcranial magnetic stimulation for migraine: a safety review. Headache. 2010;50(7):1153-1163. doi: 10.1111/j.1526-4610.2010.01697.x.

[134] Barker AT, Shields K. Transcranial Magnetic Stimulation: Basic Principles and Clinical Applications in Migraine. Headache. 2017 Mar;57(3):517-524. doi: 10.1111/head.13002. Epub 2016 Dec 28. PMID: 28028801.

[135] Clarke BM, Upton AR, Kamath MV, Al-Harbi T, Castellanos CM. Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain. 2006 Oct;7(5):341-6. doi: 10.1007/s10194-006-0329-8. Epub 2006 Oct 25. PMID: 17058041; PMCID: PMC3468174.

[136] Mohammad YM, Kothari R, Hughes G, Krumah MN, Fischell S, Fischell R, et al. Transcranial magnetic stimulation (TMS) relieves migraine headache. Headache. 2006;46:839.

[137] Mohammad YM, Hughes G, Krumah MN, Fischell S, Fischell R, Ruppel R, Schweiger J. Self-administered transcranial magnetic stimulation (TMS) during the aura phase improves and aborts migraine headache. Eur J Neurol. 2006 Sep;13:247.

[138] Bhola R, Kinsella E, Giffin N, et al. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: evaluation of outcome data for the UK post market pilot program. J Headache Pain. 2015;16:535. doi: 10.1186/s10194-015-0535-3.

[139] Starling AJ, Tepper SJ, Marmura MJ, Shamim EA, Robbins MS, Hindiya N, Charles AC, Goadsby PJ, Lipton RB, Silberstein SD, Gelfand AA, Chiacchierini RP, Dodick DW. A multicenter, prospective, single-arm, open-label, post-market, observational study to evaluate the use of sTMS in reduction of migraine headache (ESPOUSE Study). Cephalalgia. 2018;0(0):I-II. DOI: 10.1177/0333102418762525.

[140] Lammbru G, Hill B, Lloyd J, Al-Kaisy A, Andreou AP. Single-pulse Transcranial Magnetic Stimulation (sTMS) for the Treatment of Migraine: A Prospective Real World Experience. Cephalalgia. 2018;38(I S):150.

[141] Lloyd JO, Hill B, Murphy M, Al-Kaisy A, Andreou AP, Lambru G. Single-pulse transcranial magnetic stimulation for the preventive treatment of difficult-to-treat migraine: a 12-month prospective analysis. J Headache Pain. 2022;23:63. doi: 10.1186/s10194-022-01428-6.

[142] Bhola R, Kinsella E, Weatherby S, et al. Use of single pulse TMS (sTMS) to treat migraine with medication overuse. Abstract, IHC 17th Congress of the International Headache Society; May 14-17, 2015; Valencia, Spain.

[143] The manufacturing company, eNeura, remains a start-up. Its growth plan includes conducting additional Class I level investigations. Their current focus in the US is the Veteran population, and discussions regarding treating migraine co-morbidities such as TBI with sTMS are underway. (Personal communications with eNeura's sales VP, Eric Bohlen, 12/28/2024).

[144] Irwin SL, Qubty W, Allen E, Patniyot I, Goadsby PJ, Gelfand AA. Transcranial Magnetic Stimulation for Migraine Prevention in Adolescents: A Pilot Open-Label Study. Headache. 2018. doi: 10.1111/head.13284.

[145] Andreou AP, Holland PR, Akerman S, Summ O, Fredrick J, Goadsby PJ. Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine. Brain. 2016 Jul;139(Pt 7):2002-14. doi: 10.1093/brain/aww118. Epub 2016 May 30. PMID: 27246325; PMCID: PMC4939700.

[146] Lloyd JO, Chisholm KI, Oehle B, Jones MG, Okine BN, Al-Kaisy A, Lambru G, McMahon SB, Andreou AP. Cortical Mechanisms of Single-Pulse Transcranial Magnetic Stimulation in Migraine. Neurotherapeutics. 2020 Oct;17(4):1973-1987. doi: 10.1007/s13311-020-00879-6. PMID: 32632772; PMCID: PMC7851313.

[147] Lloyd JO. Investigations of mode of action of single pulse Transcranial Magnetic Stimulation (sTMS) in animal models and effectiveness in migraine patients. Doctoral thesis, Headache Research Group, Wolfson Centre for Age Related Diseases, King's College, London. 1 Sept 2021. Available at: https://kclpure.kcl.ac.uk/ws/portalfiles/portal/162487777/2021_Lloyd_Joseph_1679458_ethesis.pdf.

[148] Amiri P, Kazeminasab S, Nejadghaderi SA, Mohammadinasab R, Pourfathi H, Araj-Khodaei M, Sullman MJM, Kolahi AA, Safiri S. Migraine: A Review on Its History, Global Epidemiology, Risk Factors, and Comorbidities. Front Neurol. 2022 Feb 23;12:800605. doi: 10.3389/fneur.2021.800605. PMID: 35281991; PMCID: PMC8904749.

[149] GammaCore (nVNS) received emergency FDA clearance during COVID for at-home use in known or suspected COVID positive patients with asthma unresponsive to standard of care. In Europe it is CE-marked for a host of conditions including epilepsy, IBS, reactive airway diseases (COPD, asthma, exercise-induced bronchospasm) , anxiety, and depression. HealthCanada granted gammaCore a Medical Device License for cluster headache in adults and migraines in adolescents and adults. In Australia, gammaCore is approved for sale for treating migraine, cluster headache, and hemicrania continua in adults.

[150] https://investor.electrocore.com/news-releases/news-release-details/gammacoretm-non-invasive-vagus-nerve-stimulationnvns-receives

[151] Bremner JD, Wittbrodt MT, Gurel NZ, Shandhi MH, Gazi AH, Jiao Y, Levantsevych OM, Huang M, Beckwith J, Herring I, Murrah N, Driggers EG, Ko YA, Alkhalaf ML, Soudan M, Shallenberger L, Hankus AN, Nye JA, Park J, Woodbury A, Mehta PK, Rapaport MH, Vaccarino V, Shah AJ, Pearce BD, Inan OT. Transcutaneous Cervical Vagal Nerve Stimulation in Patients with Posttraumatic Stress Disorder (PTSD): A Pilot Study of Effects on PTSD Symptoms and Interleukin-6 Response to Stress. J Affect Disord Rep. 2021 Dec;6:100190. doi: 10.1016/j.jadr.2021.100190. Epub 2021 Jul 10. PMID: 34778863; PMCID: PMC8580056.

[152] Ferstl M, Kühnel A, Klaus J, Lin WM, Kroemer NB. Non-invasive vagus nerve stimulation conditions increased invigoration and wanting in depression. Compr Psychiatry. 2024;132:152488. doi: 10.1016/j.comppsych.2024.152488.

[153] In the author's clinical practice with Veterans with TBI, PTSD, and complex headache disorders including migraine, nVNS is combined with sTMS and has demonstrated consistent positive results in reduction of all related symptoms and titrating off prescription medications for all of these co-morbidities.

[154] It is a requirement of the Veterans Administration that the patient demonstrate ability to use a device of their preference and in some cases demonstrated therapeutic response over a trial period. The nVNS device in particular has this requirement and the company provides the demo units at no charge to complete the trial.

[155] Personal communications with Peter Saats, MD of Electrocore makers of gammaCore. (December 18, 2024)

[156] Headaches in Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 3. Obstet Gynecol. 2022 May 1;139(5):944-972. doi: 10.1097/AOG.0000000000004766. Erratum in: Obstet Gynecol. 2022 Aug 01;140(2):344. doi: 10.1097/AOG.0000000000004878. PMID: 35576364.

[157] Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153. Epub 2021 Jun 23. PMID: 34160823.

[158] Harris L, O'Connell T, Woolley JJ, L'Italien G, Martin T, Coric V, Moren JA. Observational Analysis of the Costs Associated with Acute Treatment of Breakthrough Migraine Attacks in Medicaid Patients Using Preventive Therapies. Adv Ther. 2023 Mar;40(3):1141-1152. doi: 10.1007/s12325-022-02386-w. Epub 2023 Jan 17. PMID: 36648736; PMCID: PMC9988741.

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