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Peripheral Neuromodulation for the Management of Headache

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Abstract

Context: Neuromodulation is an expanding field of study for headache treatment to reduce pain by targeting structures within the nervous system that are commonly involved in headache pathophysiology, such as the vagus nerve (VNS), occipital nerves, or sphenopalatine ganglion (SPG) for stimulation. Pharmaceutical medical therapies for abortive and prophylactic treatment, such as triptans, NSAIDs, beta-blockers, TCAs, and antiepileptics, are effective for some individuals, but the role that technology plays in investigating other therapeutic modalities is essential. Peripheral neuromodulation has gained popularity and FDA approval for use in treating certain headaches and migraine headache conditions, particularly in those who are refractory to treatment. Early trials found FDA approved neurostimulatory implant devices, including *Cephaly* and *SpringTMS*, improved patient-oriented outcomes with reductions in headaches per month (frequency) and severity.

Evidence Acquisition: This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990 - 2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

Results: The first noninvasive neurostimulator device approved for migraine treatment was the Cefaly device, an external trigeminal nerve stimulation device (e-TNS) that transcutaneously excites the supratrochlear and supraorbital branches of the ophthalmic nerve. The second noninvasive neurostimulation device receiving FDA approval was the single-pulse transcranial magnetic stimulator, *SpringTMS*, positioned at the occiput to treat migraine with aura. GammaCore is a handheld transcutaneous vagal nerve stimulator applied directly to the neck at home by the patient for treatment of cluster headache (CH) and migraine. Several other devices are in development for the treatment of headaches and target headache evolution at different levels and inputs. The Scion device is a caloric vestibular stimulator (CVS) which interfaces with the user through a set of small cones resting in the ear canal on either side and held in place by modified over-ear headphones. The pulsante SPG Microstimulator is a patient-controlled device implanted in the patient's upper jaw via an hour-long oral procedure to target the sphenopalatine ganglion. The occipital nerve stimulator (ONS) is an invasive neuromodulation device for headache treatment that consists of an implanted pulse generator on the chest wall connected to a subcutaneous lead with 4 - 8 electrodes that is tunneled the occiput.

Conclusions: The aim of this review is to provide a comprehensive overview of the efficacy, preliminary outcomes, and limitations of neurostimulatory implants available for use in the US and those pending further development.

Keywords: Peripheral Neuromodulation, Headache, Vagus Nerve, Occipital Nerves, Sphenopalatine Ganglion

1. Context

Headache is one of the leading causes of disability and reduced productivity worldwide. Headache characterizes nonspecific pain localized to the face and scalp that can present in different forms (1). Migraines typically present as a debilitating class of headache – unilat-

eral, pulsatile, and associated with nausea, vomiting, and sensitivity to light and sound, lasting upwards of minutes to hours. Some can present with prodromal aura, typically neurological manifestations such as visual disturbances with various individual triggers (2). The prevalence of chronic daily headache internationally is 4%, with females reporting more than twice as often as males (3). The American Journal of Medicine (AJM) reports lifetime prevalence of headache as 96%, with the most common classifications as tension-type headache and migraine, both more commonly seen in women (3). In collaboration with the nonprofit, WHO, Lifting the Burden, demonstrated that headaches create a significant economic burden from decreased productivity, increased sick days, and disability costs (4, 5). A recent health surveillance study conducted by the CDC lists migraine and headache among top emergent complaints, accounting for nearly 4 million ED visits in the United States in 2014 (6, 7).

The main classifications of headache include migraine, tension-type headache (TTH), cluster headache, and secondary causes of headache – either underlying systemic or neurologic disease (2, 8). TTH is the most prevalent form of headache, and nonspecific in comparison to migraine, often presenting bilaterally without pulsatile features (2). Cluster headache is among the least common, often idiopathic, unilateral, with occasional ocular pain and autonomic symptoms (2). The pathophysiology of headache is likely to be mediated by vasodilation of arteries and cervical nerve root delivery of pain mediated signals. Recent literature discusses the role of thalamo-cortical circuits in the premonitory stages of headache and the release of neuropeptide headache mediators such as calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP) (9). New therapies include targeting the early signaling for prophylactic treatment of headache and modulating neuropeptide levels for pain management.

Abortive and prophylactic treatments of headache constitute the mainstay of therapy for both migraine and headache. Beta-blockers, TCAs, and antiepileptics are common evidence-based prophylactic medication while triptans and NSAIDs function as abortive agents (9). Occipital nerve blocks and onabotulinim toxin A injections are gaining popularity as non-pharmaceutical options for chronic headache pain management and dietary and lifestyle changes to avoid triggers. Behavioral therapy is an important treatment modality that incorporates biofeedback and CBT for relaxation and pain modulation (10).

2. Evidence Acquisition

This was a narrative review. The sources for this review are as follows: Searching on PubMed, Google Scholar, Medline, and ScienceDirect from 1990-2019 using keywords: Peripheral Neuromodulation, Headache, vagus nerve, occipital nerves, sphenopalatine ganglion.

3. Results

3.1. Neuromodulation for Headaches

Neuromodulation is an expanding field of study for headache treatment aimed at noninvasive therapy to reduce pain by targeting structures within the nervous system commonly involved in headache pathophysiology, such as the vagus nerve (VNS) or sphenopalatine ganglion (SPG) for stimulation (11, 12).

3.1.1. Mechanism of Action

Neuromodulation combines biomedical engineering and neurophysiology to optimize neuronal function and aid in the treatment of pathological processes such as pain and movement disorders. It is broadly defined as "the process of inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral, or autonomic nervous systems" (13). It can be divided into electrical and chemical modes of delivery, where electrical provides stimulation to muscles and nerves, and chemical often utilizes implants for local delivery through epidural and intrathecal placements. For its application to chronic pain, neuromodulation capitalizes on the gate control theory to provide relief in narcotic refractory conditions by delivering a stimulus to denervated or deafferented pain areas to help reprogram the brain's response to pain (14).

3.1.2. Indications

One of the main indications for neuromodulation therapy is pain management. "[…] are used for a growing number of indications including pain (ischemic, visceral, and neurogenic), angina pectoris, peripheral vascular disease, epilepsy, urinary disorders, spasticity from spinal cord injury, cerebral palsy, or multiple sclerosis, and diabetes" (15). Several advances in therapy include ONS for chronic migraine relief and VNS for seizures and intractable epilepsy refractory to surgery. Neuromodulation is also considered in conditions refractory to other medical treatment and/or in conjunction with that treatment to enhance pain control effects. However, there are some limitations to its availability, due to access and cost, and its rarity in usage as a standard treatment approach.

3.1.3. Patient Selection

As pain is not a discriminatory pathology, any age or gender can be affected and thus eligible for neuromodulation for therapeutic management. The majority of migraine sufferers are women, children, and patients who have a familial prevalence. The intensity of migraines is often individually elicited, but those particularly sensitive to triggers and otherwise benign stimuli would benefit. Those who suffer from chronic pain and chronic comorbidities would benefit the greatest, but use in terminal conditions is potentially financially burdensome and would require further quality measure workup. Due to the nature of the device's implantation, the patient would also have to pass a pre-op evaluation and be a good surgical candidate. The treatment works best in enhancing existing responsiveness to conventional therapies, such as abortive migraine therapy, but also in refractory cases. Another major component in determining eligibility is psychological attitude towards the treatment. There is the postulation that the belief or willingness in the treatment to work dramatically affects outcomes and duration of relief (16, 17).

3.2. Currently Available Devices

3.2.1. Transcutaneous Supraorbital Neurostimulator

The first noninvasive neurostimulator device approved for migraine treatment was the Cefaly device. The Cefaly device is an external trigeminal nerve stimulation device (e-TNS) that transcutaneously excites the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) via a bipolar self-adhesive electrode (30 x 94 mm) applied to the forehead. The device is a constant current generator with a maximum skin impedance of 2.2 kΩ. Rectangular biphasic symmetrical pulses zero are delivered with a progressively increasing intensity from 1 to 16 mA over 14 minutes. Cefaly was the first medical device FDA approved for migraine prophylaxis in 2014, which has since been renamed Cefaly PREVENT. In 2017, the Cefaly ACUTE device was released as an FDA approved acute migraine therapy. The Cefaly DUAL device was also released, which combines both acute and preventative settings. Cefaly PREVENT requires daily, low-frequency, short treatment sessions, whereas Cefaly ACUTE applies a high-frequency, long treatment session. It is hypothesized that the patient's belief in or willingness toward the success of the treatment can dramatically affect patient outcomes and duration of migraine relief (18, 19).

Since 2008, clinical studies of the efficacy and mechanism of action of Cefaly have been performed. The PREvention of Migraine using Cefaly (PREMICE) study was the first prospective, multicenter, randomized, and sham-controlled trial of the device (20). Published in 2013, the PREMICE study found a greater therapeutic gain of eTNS compared to pooled results of placebo-controlled trials of topiramate (26.1% vs. 23.5%). Although topiramate is more effective than eTNS in reducing migraine days, the safety:efficacy ratio of Cefaly is superior. A follow-up survey of 2,313 headache patients who underwent a 40-day trial of Cefaly found it to be safe and well-tolerated, with only 4.3% of subjects reporting adverse events (21). The adverse events reported with the Cefaly were all minor and reversible, like forehead paresthesia (20). Trials of topiramate had 25% of patients stop therapy due to more significant intolerable side effects, including fatigue, insomnia, and nausea (22). Since Cefaly does not have as wide-ranging and severe side effect profile, eTNS is an attractive option for patients unwilling or unable to use anti-migraine drugs.

A subsequent smaller study (n = 24) demonstrated efficacy of brief, high-frequency Cefaly treatment in patients who had never used preventative medications, suggesting Cefaly could be a first line treatment for low-frequency migraineurs (23). A 2017 study found Cefaly to be effective in reducing number of migraine days, intensity, and acute medication use in both chronic and episodic migraine in topiramate-refractory migraineurs (24). In an open-label study of Cefaly used as an acute treatment in chronic migraine with or without medication overuse disorder, treatment was found to reduce pain and medication consumption (25). These studies did not demonstrate significant differences in pain relief between migraine type or the presence of medication overuse. A separate prospective, non-randomized study showed similar efficacy of Cefaly in other types of primary headache (26). The ability of Cefaly to improve patient outcomes in a clinically heterogeneous patient population reflects the versatility of eTNS.

An open-labeled pilot trial evaluating Cefaly as an acute migraine treatment showed an average reduction of headache pain severity by 57.1% after a 1-hour e-TNS treatment, with 76.7% of patients reporting $\geq$ 50% pain relief (27). This prompted a randomized, double-blind, sham-controlled trial: the ACME study (ACute treatment of Migraine with External trigeminal nerve stimulation). The results showed e-TNS during a migraine attack caused a significant reduction in mean headache intensity at multiple time points than sham treatment (28).

Cefaly represents an FDA-approved option for both acute and preventive treatment that can safely be used as monotherapy or in combination with medication. However, it is important to consider the limitations of the available studies. Shortcomings of the clinical trials to date include clinical heterogeneity of migraine type, duration of illness, and medication usage. Each study addressed the differences present in their patient populations and per-

formed subgroup analyses, which found these differences did not significantly affect outcomes. The headache location was not considered, which may be worth investigating due to the variability between migraineurs. Compliance has been less in Cefaly trials compared to drugs. One study reported 40% of patients used it the appropriate amount of time, and 4.4% did not use it all (21). However, the satisfaction rate was 53.4% and reached 70.6% in the PREMICE trial (20). More extensive randomized-controlled trials (RCT) are necessary to fully define the versatility of Cefaly eTNS application in migraine treatment.

3.2.2. SpringTMS

The second noninvasive neurostimulation device receiving FDA approval was the single-pulse transcranial magnetic stimulator, *SpringTMS* (sTMS). The 1.5 kg handheld device (81 mm; W: 220 mm; D: 134 mm) is positioned on the occiput and the patient presses a button to deliver a single magnetic pulse of 0.9 T. The electrical current generated causes electromagnetic induction of neurons over the target area of the device. Pre-clinical models have investigated the mechanism of action of transcranial magnetic stimulation and suggest modulation of thalamocortical signaling, opioidergic activity, and suppression of cortical spreading depression are the primary mechanisms (29, 30). First approved in 2014 for acute migraine with aura treatment, sTMS indications have since expanded to include acute and preventative treatment of migraine with or without aura.

The first randomized, sham-controlled trial of sTMS demonstrated pain relief at 2 h post-sTMS treatment compared with sham stimulation and sustained relief at 24 h and 48 h after treatment (31). After introducing the *SpringTMS* device in the UK, a post-market pilot program demonstrated a possible preventative benefit for migraine with and without aura, prompting further investigation by the eNeura *SpringTMS* Post-Market Observational U.S. Study of Migraine (ESPOUSE) (32, 33). The preventive treatment included the delivery of four pulses twice daily, and the acute treatment was a maximum of three treatments of three pulses per attack. ESPOUSE was a multicenter, prospective, open label observational study that had patients undergo three months of preventative and acute migraine treatment. The ESPOUSE study demonstrated similar outcomes compared to the post-market UK observational data with a 50% reduction in headache days in 46% and 47% of patients. These outcomes were achieved in different populations (US versus UK) with different investigators indicating the consistency of sTMS efficacy. Both studies found sTMS to be well-tolerated with a mild side effect profile. The most common side effect reported was light headedness.

TMS's safety has been well-established as it has been used for decades diagnostically and therapeutically for a range of neurological and psychiatric disorders (34). In 2017, the FDA approved sTMS for acute and preventative migraine treatment and expanded clearance to children 12 years of age and older based on the demonstrated safety profile and efficacy in the EPOUSE study and a pilot open-label study in adolescents (35). The adolescent study did not show a significant reduction in acute medication use nor in moderate/severe pain days in the paired analysis. Still, it did show 4.5 fewer headache days per month.

Contraindications to sTMS include the presence of other signaling devices like cardiac pacemakers or metal implants. Limitations of published studies to date on sTMS are similar to those of eTNS, including clinical heterogeneity and small sample sizes. The greatest limitation to ESPOUSE is the lack of a sham control. Successful sham-controlled studies exist for tSNS and in the sTMS study for acute migraine treatment (20, 28). The authors of ESPOUSE explain creating a true sham for a preventive treatment, which requires multiple treatments per day, makes maintaining blinding difficult. An additional limitation to ESPOUSE is the lack of subgroup analyses to account for differences of migraine type (episodic/chronic and with/without aura) (33). No published studies exist for sTMS in medication overuse or comparison to common anti-migraine drug therapy like topiramate, unlike eTNS literature (24). Due to the demonstrated efficacy in migraine treatment and favorable safety profile, sTMS represents a well-tolerated, noninvasive, non-pharmacologic migraine therapy. Similar to the evidence for eTNS, more rigorous randomized controlled trials are needed to elucidate the efficacy across the heterogenous migraineur population and long-term safety of sTMS.

3.2.3. GammaCore

GammaCore is a handheld transcutaneous vagal nerve stimulator applied directly to the neck at home by the patient for treatment of cluster headache (CH) and migraine. The device is programmed for two-minute electrical stimulation cycles and can be used at the onset of an attack or prophylaxis. The initial iteration of the gammacore device contained a charge for 300 treatment cycles, after which a new device had to be purchased. The newer device comes with a programmable card that reloads charges onto the device (36). To deploy the device, the user applies gel to the stimulation tips, locates their carotid pulse on either side of their neck, and depresses the device directly over that site. A slight downward tug of the user's ipsilateral lip typically indicates target intensity, which is modulated by a wheel on the side of the device (37).

The cervical branch of the vagus nerve is the target area

for treatment (38). Inputs from the vagus nerve connect to various higher levels in the brain, and inhibiting afferents into the caudal trigeminal nucleus. The trigeminal-autonomic reflex pathway connects the autonomic afferents of the vagus to the nerve to the pain locus at the trigeminal nerve.

The Acute Treatment of Cluster Headache study, ACT1 and ACT2, found that gammacore as an adjunct to standard of care (SoC) treatment was superior to SoC alone in episodic cluster headache. A cost analysis using a one-year time horizon found an approximately $500 cost savings for gammacore plus SoC versus SoC alone. Quality of life gains were seen in addition to the cost savings and increased efficacy (39).

The PREVention and acute treatment of chronic cluster headache (PREVA) study demonstrated a quality of life gains in addition to cost savings and increased efficacy in chronic cluster headache. Gammacore, approved by the FDA in April 2017, is currently subject to reimbursement policies on par with invasive implanted vagus nerve stimulator devices. Ultimately, leading to a scenario where device acquisition is difficult for patients (40).

Current CH SoC has many drawbacks. Triptan overuse in cCH is common, and high flow oxygen is logistically impractical. Difficulties with high flow oxygen include reimbursement, portability and fire hazard, and is impractical except for nocturnal attacks. Suboccipital corticosteroid injections, also viewed as fairly standard treatment, are subject to many drawbacks as well. This includes treatment by a professional at a medical setting and long-term effects such as Cushing syndrome, blood glucose elevation, and increased risk for avascular necrosis of the femoral head. Prophylactic medications such as verapamil and lithium maintain high levels of safety and tolerability issues (3).

GammaCore is not as widely studied in migraine, however, initial results have proven promising. A study evaluating acute migraine treatment in adolescents found that 46.8% (22/47) did not need rescue medications when using the gammacore device, and treatment was well tolerated (41).

The vagus nerve is a major parasympathetic branch of the autonomic nervous system. Eighty percent of the nerves are afferent projections to the nucleus tractus solitarius (NTS) of the brainstem. The vagus nerve has been a treatment target for over 20 years in epilepsy with iVNS devices. Another stimulator, Nemos, has attempted to target the vagus nerve at its auricular branch at the concha of the ear. Transcutaneous stimulation was postulated to require too much current to alter A and B fibers and thought to be too big of a hurdle to provide pain modulating treatment. The energy produced by gammaCore is pulsed to produce an alternating sine wave current, allowing for fifteen times greater energy transfer compared to implantable models, all while eliciting minimal nociceptive pain (42).

3.3. Non-FDA Approved Devices

3.3.1. The Scion Device (Caloric Vestibular Stimulator)

Several other devices are in development to treat headache and target headache evolution at different levels and inputs. The Scion device is a caloric vestibular stimulator (CVS) used for 20 minutes once or twice a day. The device interfaces with the user through a set of small cones resting in the ear canal on either side and held in place by modified over-ear headphones. An element with the device heats and cools the cones causing an alteration in vestibular nerve conduction (43).

Standard CVS employs water or air and is difficult for home use. The Scion Device employs a solid-state element to create thermal waveforms. Thermal variation causes density changes in endolymphatic fluid. CVS affects the brainstem pacing center autoregulatory center and initiates the vestibulo-ocular reflex, causing horizontal nystagmus. Additionally, CVS alters cerebral blood flow velocity. Migraine etiology involves cerebral blood flow dysregulation and brainstem dysfunction. The Scion Device seeks to modify these two aspects of migraine pathology. A small pilot project attempted to evaluate the feasibility of at-home use. Three migraineurs who participated in the trial all reported a decreased number of headaches (44).

A subset of the migraine population features vertiginous symptoms during attacks increasing interest in the role that vestibular inputs may play in migraine pathology. In the U.K., a larger study at the University of Kent had 81 volunteers with episodic migraine, using a protocol of CVS for 2 minutes every day over a three-month timespan. The study saw decreased frequency and severity during the trial (45).

An additional trial is currently ongoing and hopes to use a CVS device for thermoneuromodulation to treat substance abuse disorder. It is an interventional, randomized, single-blind, sham-controlled study with 24 participants at Wake Forest Medical Center. Participants receive CVS or sham therapy twice daily over five days. Trial participants receive pre and post mood and substance use questionnaires, in addition to structural and functional MRI and urine drug screens (46).

3.3.2. Sphenopalatine Ganglion (SPG) Stimulator Pulsante

The sphenopalatine ganglion (SPG) has long been a target for headache treatment. The pulsante SPG Microstimulator is a device implanted in the upper jaw via an hour-long oral procedure. The microstimulator is controlled by

a patient-controlled handheld remote and features no battery. The device is powered by induction via radiowaves emitted by the handheld device. Initial studies have reduced episodic clusters in 85 patients by 68% concerning frequency and intensity. A lead of the stimulator is placed into the pterygopalatine fossa under CT guidance to ensure proper midface location. The Pathway CH-1 and Pathway R-1 studies have sought to evaluate the efficacy of sphenopalatine ganglion stimulation in the treatment of 99 patients with cluster headache.

Thirty-three patients in the Pathway CH-1 over 24 months saw a 50% or greater acute effectiveness or 50% or greater reduction in frequency. In total, 5961 attacks were recorded. Forty-five percent of participants were acute responders, with 78% of those patients employing stimulator monotherapy. Additionally, 33% saw a decrease in the frequency of attacks. In total, 61% (20/33) saw a reduction in intensity, frequency, or both. The majority of participants saw maintained benefits throughout the 24-month study. SPG stimulation seeks to treat a cohort of mostly disabled patients who have seen high treatment failure rates with medication that can be both challenging to tolerated and inconvenient. Sham control in the CH-1 trial lowers the likelihood of treatment benefit due to surgical response of implanting the device itself.

Thirty percent improvement is typically used as a threshold for tension, headache, and migraine. Since cCH is so debilitating, evaluating cCH treatment with such a threshold may be reasonable. When evaluating with a thirty percent improvement threshold, eighty percent of participants found benefit with treatment. Over the 24 months, 2 of 33 participants are no longer having attacks, effectively converting from cCH to eCH. During the trial, some concern was raised over increased contralateral attacks; however, half of the 11 patients experiencing contralateral attacks had a prior history (47).

Using data from the Pathway R-1 Registry, a 1-year cost analysis was performed and a significant cost savings of approximately 41-51% was seen using German medication prices in 2016. Acute medication savings contribute to 97% of that cost savings (48).

Paresthesia and pain in the maxillary area were the primary side effects seen related to the device's placement. These side-effects decreased significantly over several months, yet the positive effects have remained over time in longer-term studies (49). Trials employing a temporary electrode placed in the pterygopalatine fossa for migraine attacks appear less promising (50).

Smaller trials with seven patients using trigeminal or SPG stimulation with or without peripheral stimulation and temporary lead placement via lateral transpterygoid are being performed. Trigeminal stimulation via subtemporal craniotomy to meckel's cave limits V3 involvement and masseter contraction as opposed to the Hartel approach (51).

A small trial of 59 participants with cCH were implanted with bilateral SPG and continuous stimulation. Some saw daily to less than one per week attacks and discontinued previous medication regime (52). A high frequency of 120 hz or greater is thought to cause depletion of neurotransmitters in efferent parasympathetic nerves. Stimulation of the peripheral autonomic ganglion could affect a centrally mediated disorder via feedback mechanisms or depletion of parasympathetic NTs (53).

The SPG is a peripheral bundle of nerves containing autonomic, sensory, and motor neurons located in an inverted 2cm by 1cm pyramid-shaped space posterior to the nasal cavity. This specific collection of nerves is implicated in a diverse range of processes that, when dysfunctional, are implicated in headache generation. The SPG simulation allows for modulation of neurogenic inflammatory pathways, the trigeminovascular system, and the parasympathetic system (54). Neuromodulation holds a distinct advantage with its ability to be flexible and reversible.

3.3.3. Occipital Nerve Stimulator

An invasive neuromodulatory device for headache treatment that has been investigated is the occipital nerve stimulator (ONS). The device consists of an implanted pulse generator on the chest wall connected to a subcutaneous lead with 4-8 electrodes that is tunneled the occiput. The patient applies stimuli with a handheld remote control. Before permanent implantation, neurostimulation is trialed for up to two weeks. If greater than 50% pain reduction is achieved, a permanent implantation may be pursued. The mechanism of action of ONS is incompletely understood but is suggested to be a combination of peripheral and central neuromodulation (55, 56).

The efficacy of ONS has been studied in the prevention of medication-refractory cluster headache and migraine. Randomized, sham-controlled trials have evaluated ONS over a 3-month treatment period. The ONSTIM study reported a 39% responder rate in the ONS treatment group, which is comparable to topiramate's response rate (57). Despite the limitations of this study, including a short observation period and possible unblinding of the preset stimulation group, the authors concluded that ONS was relatively safe and warranted further study.

A larger-scale randomized, sham-controlled study did not achieve the primary outcome of at least 50% pain reduction at three months. Still, it did achieve secondary endpoints (30% reduction in pain scores, number of headache days, and migraine-related disability) (58). Adverse events related to the device in these two studies were

not uncommon, including lead migration and infection with some patients requiring hospitalization or surgical intervention. The PRISM study was the third multicenter study, published only in abstract form, which found no significant difference in the primary end point of the number of migraine days per month between the randomized ONS and sham groups (59). A recent long-term prospective study of ONS in refractory chronic migraine patients with a 7-year follow-up period found substantial pain reduction (VAS -4.9 $\pm$ 2.0 points) in ONS patients (60). Complete resolution of attacks by the final follow-up visit was achieved in 5/35 patients. Although limited by the uncontrolled and open-label study design, these results suggest a sustainable benefit in refractory chronic migraine.

Initial open-label studies in medication refractory chronic cluster headache patients showed improvement with ONS (61, 62). Recent open-label studies of ONS in refractory chronic cluster headache have found ONS to maintain safety and efficacy over the long-term. One study with a follow-up period of six years had 66% of patients achieve at least a 50% reduction in headaches per day. One-third were non-responders, and half of these patients had previously been responders before developing tolerance (63). Another study with a mean follow-up period of 39 months had a response rate of 52.9% and a 62% drop in triptan usage (64). ONS also improved functional and emotional improvements measured by HIT-6, MIDAS, and HAD scales in a prospective observational study (65).

Investigation of ONS for application in occipital neuralgia is limited to case series. In a recent retrospective review, ONS's success rate was 85%, with a significant reduction in pain score (66). Another long-term study of ONS in intractable chronic unilateral neuralgiform headache had a 77% response rate (at least 50% reduction in daily attack frequency) with reduction in attack severity and duration (67).

Unlike noninvasive neurostimulator devices, ONS is not FDA approved and incurs greater out-of-pocket costs. Due to the prohibitive cost and potential adverse events with invasive ONS, this treatment modality is recommended to be reserved for only the most severely affected refractory headache patients. The limited number of randomized-controlled trials and heterogeneity of outcome measures between studies offers a low to moderate level of evidence for ONS, but the demonstrated ability to affect positive change in the most refractory headache patients warrants continued research.

4. Discussion

Neuromodulation is an expanding field of study for headache treatment aimed at noninvasive therapy to reduce pain by targeting structures within the nervous system commonly involved in headache pathophysiology, such as the vagus nerve (VNS) or sphenopalatine ganglion (SPG) for stimulation (11). The first noninvasive neurostimulator device approved for migraine treatment was the Cefaly device. The Cefaly device is an external trigeminal nerve stimulation device (e-TNS) that transcutaneously excites the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) via a bipolar self-adhesive electrode (30 x 94 mm) applied to the forehead. Larger randomized-controlled trials (RCT) are necessary to fully define the versatility of Cefaly eTNS application in migraine treatment. The second noninvasive neurostimulation device receiving FDA approval was the single-pulse transcranial magnetic stimulator, *SpringTMS* (sTMS). Similar to the evidence for eTNS, more rigorous randomized controlled trials are needed to elucidate the efficacy across the heterogenous migraineur population and long-term safety of sTMS. GammaCore is a handheld transcutaneous vagal nerve stimulator applied directly to the neck at home by the patient for treatment of cluster headache (CH) and migraine. GammaCore is not as widely studied in migraine, however, initial results have proven promising.

Several other non-FDA-approved devices are in development to treat headache and target headache evolution at different levels and inputs. They require more research in different age populations to be considered as prescribed treatments. The Scion device is a caloric vestibular stimulator (CVS) used for 20 minutes once or twice a day. The device interfaces with the user through a set of small cones resting in the ear canal on either side and held in place by modified over-ear headphones. The sphenopalatine ganglion (SPG) has long been a target for headache treatment. The pulsante SPG Microstimulator is a device implanted in the upper jaw via an hour-long oral procedure. And finally, the occipital nerve stimulator (ONS). The device consists of an implanted pulse generator on the chest wall connected to a subcutaneous lead with 4-8 electrodes that is tunneled the occiput.

4.1. Limitations of Therapy

While there have been promising initial results from invasive and noninvasive neuromodulation devices for headache, there is still much about the mechanism that is unknown. Pending completion of further pilot trials, clinical trials in controlled settings are required for many of these devices to receive FDA approval for use in provider settings as an abortive or prophylactic treatment beyond refractory intervention. Transcranial magnetic stimulation has been FDA approved for use in patients with migraines with aura as abortive therapy and is now expanding for approval in chronic migraines (19). The upfront cost

of interventional management is often offset in the long term with reduced use of pharmaceutical agents; however, most neuromodulatory procedures are indicated only in refractory cases (36). Several studies aimed at improving lead placement for ONS to reduce adverse events associated with lead migration post implantation; however, this specialized technique can serve as a barrier to the ability of providers to offer neuromodulation as a common therapy (68). Further ongoing studies on neuromodulation are investigating the specified targets and mechanisms of action of treatment. Much of this updated technology is new, and the long-term impact is not yet clear (69). Additional limitations include surgical error, adverse events, individualized patient response to therapy, and patient user error.

5. Conclusions

Headache and migraine headache are well-established diagnoses with a significant associated worldwide economic burden to the patient and society. While pharmaceutical medical therapies for abortive and prophylactic treatment, such as triptans, NSAIDs, beta-blockers, TCAs, and antiepileptics, are effective for some individuals, the role that technology plays in investigating other therapeutic modalities is important. Peripheral neuromodulation has gained popularity and FDA approval for use in the treatment of certain headache and migraine headache conditions, particularly in those who are refractory to treatment. In this review, we examined the methodology, efficacy, preliminary outcomes, and limitations of several clinical trials of different neurostimulatory implants, including the Cefaly Cranial Nerve Stimulator, *SpringTMS*, gammaCore, Scion Device, SPG Stimulator Pulsante, and the ONS. Early trials found FDA approved devices *Cephaly* and *SpringTMS* to improve patient-oriented outcomes such as reductions in headaches per month (frequency), and severity, but with limitations in sample size and heterogeneity of study population.

Footnotes

Authors' Contribution: Author Contributions: Study concept and design: IU, RS, DS, LK analysis; interpretation of data: IU, RS, DS, LK, SV, VO, EC; drafting of the manuscript: SV, VO, EC, LM, AK; critical revision of the manuscript for important intellectual content: EC, LM, AK, FI, GV, OV.

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