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REGENERATIVE PAIN MEDICINE/INTERVENTIONAL PAIN MEDICINE (E CORNETT BRADLEY, SECTION EDITOR)

Occipital Nerve Stimulation: An Alternative Treatment of Chronic Migraine

Benjamin S. Maxey[1] · John W. Pruitt[1] · Ashley Deville[1] · Carver Montgomery[1] · Alan D. Kaye[2] · Ivan Urits[2,3]

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Abstract

Purpose of Review This paper will examine the efficacy and safety of occipital nerve stimulation as a non-pharmacological alternative treatment for migraine.

Recent Findings Migraine is characterized as a primary headache disorder with possible premonitory and aura phases, both of which vary greatly in symptomatology. The most common treatments for chronic migraine are pharmacological and are aimed at both acute relief (e.g., nonsteroidal anti-inflammatory drugs, triptans, and ergots) and prophylaxis (e.g., propranolol, valproic acid, and topiramate). For patients with medically refractory migraine, acute relief medication overuse can increase the risk of developing more severe and more frequent migraine attacks. Occipital nerve stimulation is a non-pharmacological alternative treatment for chronic migraine, which could eliminate the risk of adverse effects from acute relief medication overuse. Neurostimulation is thought to prevent pain by blocking signal transduction from small nociceptive fibers with non-painful signaling in larger adjacent fibers.

Summary Existing data from clinical trials support the overall safety and efficacy of occipital nerve stimulation for the treatment of chronic migraine. However, few large controlled, double-blinded studies have been conducted, due to both practical and ethical concerns. Currently, occipital nerve stimulation is available as an off-label use of neurostimulation for pain prevention but is not approved by the FDA specifically for the treatment of chronic migraine.

Keywords Migraine · Primary headache disorder · Medication overuse headache · Occipital nerve stimulation · Neurostimulation

Introduction

Migraine headaches affect a significant portion of the global population and can have severe consequences on quality of life, healthcare utilization, and rate of comorbidities in those affected. It is characterized as a recurrent headache disorder that manifests in attacks lasting 4–72 h and is often associated with nausea, photophobia, and phonophobia. Current understanding classifies migraine as a disorder of sensory processing at the level of the trigeminocervical complex that is influenced by contributions from peripheral nerves and is modulated by various neuropeptides. In general, migraine is estimated to affect approximately 12% of the US population, while the prevalence of chronic migraine (defined as 15 or more headache days per month) is estimated at 0.9% to 2.2% [1]. Women experience migraine more frequently than men and represent the population with the most severe disease burden. People of lower socioeconomic status are also disproportionately affected [1].

Currently, migraine headaches have no cure, and the most common treatments are pharmacological agents. The goal of acute management is to stop active headache pain, while drugs used for prevention are reserved for those with increased frequency of migraine pain greater than twice a

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✉ Benjamin S. Maxey
bsm005@lsuhs.edu

[1] School of Medicine, Louisiana State University Health Science Center Shreveport, Shreveport, LA, USA

[2] Department of Anesthesiology, Louisiana State University Shreveport, Shreveport, LA, USA

[3] Southcoast Physicians Group Pain Medicine, Southcoast Health, Wareham, MA, USA

week. Effective drugs to stop active headaches are nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, and ergots, and commonly prescribed preventive treatments include beta-blockers (e.g., propranolol), non-dihydropyridine calcium channel blockers (e.g., verapamil or diltiazem), or anticonvulsants (e.g., valproic acid, topiramate) [2]. Botox injections, nerve blocks, and surgical decompression have also been attempted with varied success rates among individuals with drug-refractory migraine [2]. The available treatment arsenal does come with medication-related side effects and the possibility of decreased responsiveness and/or lower rates of adherence in some patients. As many as 70.2% of migraine patients treated with medication will be non-adherent to medical therapies within 6 months [3, 4].

The need for effective, safe, and long-lasting anti-migraine treatments has opened the field to non-pharmacological neurostimulation. Further study is needed to improve the options for therapeutic treatment of migraine while minimizing the incidence of medication overuse. Occipital nerve stimulation (ONS) offers a non-pharmacological alternative treatment for migraine that could avoid long-term adverse drug-related effects. ONS first found success in the treatment of occipital neuralgia [5•], but is now targeting primary headache disorders like migraine. This paper will examine the efficacy and safety of occipital nerve stimulation as a non-pharmacological alternative treatment for migraine.

Background

Pathophysiology

Migraine has a complex pathophysiology that is incompletely understood. It is principally thought of as a disorder of sensory processing that manifests through derangements of various craniovascular and neuropeptide systems. The most direct cause of migraine pain is the activation of peripheral afferent nociceptive fibers at the trigeminal ganglion, which innervate meningeal blood vessels and large cerebral arteries. The dura mater in particular has been shown to have an important role in this mechanism [6, 7]. Studies have shown that the activation of these systems by mechanical, chemical, or electrical stimuli results in headache pain that is exceedingly similar to that of migraine and can elicit classic migraine symptoms of nausea and photophobia [6, 7]. These innervations of the meninges are via C fibers and Aδ fibers with axon projections traveling through all three divisions of the trigeminal nerve, particularly the ophthalmic division. Signaling by vasoactive peptides like calcitonin gene-related peptide (CGRP), substance P, and neurokinin A has been shown to modulate the trigeminovascular pain pathways outlined above and affect the perception of migraine pain [6]. Studies showing 5-HT_{1D} receptors and CGRP in the sphenopalatine ganglion may point to a mechanism for the modulation of nociception in the trigeminovascular system and may explain why triptans are effective at relieving the symptoms of migraine [6, 8, 9]. Nerves originating from the upper cervical roots–like the greater occipital nerve–also have some innervation of the dura along with central afferent projections that may influence migraine by convergence with the trigeminal system when terminating at the spinal trigeminal nucleus caudalis [6, 10]. Convergent inputs from cervical and trigeminal afferents are referred to collectively as the trigeminocervical complex, which has been shown to play a role in migraine [6, 11, 12]. This linkage, which may have implications for the therapeutic treatment of migraine, is explored further in a later section.

Presentation and Diagnosis

Migraine attacks are classically divided into three stages: the premonitory, aura, and headache phases. Attacks can progress in a linear fashion through these phases, but not all patients fit this mold as many show overlaps of symptomatology throughout the progression of an attack. Regardless, headache always stands out as the primary feature. The premonitory phase is the most variable of stages and precedes the development of headache by up to 72 h, although some symptoms that arise during this phase may be present throughout the attack. Patients may experience changes in mood like irritability and tiredness or more obvious symptoms like fatigue, repetitive yawning, stiff neck, or phonophobia [6]. Patients often fall into a pattern of symptoms that is unique to them, which allows them to predict oncoming attacks [6].

Nearly a third of patients with migraine will experience a classic aura phase signaling an imminent attack [6]. Aura is defined by the International Classification of Headache Disorders (ICHD-3) as one or more transient neurologic symptoms that are fully reversible and resolve within an hour [13]. Visual disturbance is by far the most common type of aura, occurring in over 90% of cases, but other deficits may occur including sensory, motor, or speech [6]. Although migraine aura is poorly understood, current knowledge points to cortical spreading depression—a transient wave of neuronal depolarization of the cortex–as the mechanism underlying migraine aura [6]. Migraine may present with or without aura, but the distinguishing feature is typically headache of unilateral location, pulsatile character, and intense severity that may be associated with nausea and/or photophobia [13].

Migraine is a difficult condition to diagnose and to treat properly because of the variability in symptomatology among attacks. The first step in diagnosis is a detailed history, followed by ruling out secondary causes of headache, and establishing a pattern of attacks that is consistent with migraine. Most patients have their first point of

contact with a primary care provider, or in severe cases, an emergency department, which often leads to misdiagnosis or unnecessary testing [14]. Accurate diagnosis is best achieved by a headache expert with understanding of the classification of the disorder, but physicians with high clinical suspicion should diagnose and refer to a headache expert so that a proper treatment plan can be developed. Ineffective acute treatment has been identified as a major risk factor in progression from episodic to chronic migraine [15]. Diagnostic criteria, namely the International Headache Society (IHS) classification ICHD-3 beta, have been established to further categorize migraine into distinct patterns that improve both the accuracy of diagnosis and guide treatment. These criteria divide migraine into two diagnostic categories by the number of days in a month the patient experiences headache. Chronic migraine is defined as headache on at least 15 days per month, while episodic migraine is less than 15 headache days [1, 13].

Risk Factors

As migraine, especially the chronic form, is associated with serious socioeconomic and health-related quality of life consequences, identifying and cataloging known risk factors is of great importance [1]. The study of risk factors has focused on identifying environmental, behavioral, and genetic factors that increase the risk of progression from episodic to chronic migraine. The most important factors identified in this process are overuse of acute migraine relief medication, ineffective acute treatment, obesity, depression, and recent stressful life events [15]. Of these mentioned, overuse of acute relief medication such as analgesics and triptans is likely the most important risk factor for progression to chronicity [1]. ICHD classifies medication overuse as analgesic use on greater than 15 days per month or triptans on greater than 10 days per month [13]. Regular overuse is associated with increased headache days and progression to diagnosis of chronic migraine [1]. Studies have shown that patients who discontinue medication overuse have substantial relief of headache and improved effectiveness of prophylactic medications [16].

Genetics research in the form of genome-wide association studies (GWAS) has provided new insight on how various genes influence migraine pathophysiology and on the role that genetics plays in the different subtypes of migraine and their most common comorbid disorders. Common migraine (migraine with or without aura) has been found to likely be polygenic in origin. Multiple family and twin studies have shown that family history of common migraine is a strong risk factor for subsequent generations, demonstrating high penetrance and a heritability between 30 and 60% [17–20].

Epidemiology

Chronic headache disorders like migraine are one of the leading causes of disability in the USA and often affect young and otherwise healthy populations, especially women. One recent study showed that prevalence is high in the US, affecting 15.3% of the general population and 20.7% of women when results were age adjusted. Women are more than twice as likely to develop migraine as men (9.7%). By age, the highest prevalence is in 18–44-year olds at a rate of 17.9% [14]. Certain ethnic groups have also been shown to have higher prevalence of migraine and chronic headache. Prevalence is highest in native Americans, then African-Americans, followed by Caucasians and Asians [14]. Socioeconomic status has also been identified as an important predictor of migraine and chronic headache with those achieving a family income of less than $35,000 at a prevalence of 19.9% and those below the poverty line at 21.7% [14].

Occipital Nerve Involvement in Migraine

Functional connections between the trigeminal nerve and nerves originating from the high cervical roots like the greater occipital nerve (GON) have been implicated in the pathophysiology of migraine and other primary headache conditions [6]. It is unclear the extent to which nerves from the C1–C3 spinal roots contribute to the development of migraine, and a direct linkage has not been mapped. However, evidence points to the close spatial relationship between the upper cervical and trigeminal afferents at the location of the trigeminal nucleus caudalis as the mechanism of this linkage [21]. These connections, which depend on central convergence of second-order meningeal and cervical afferents, have also been implicated in the mechanism of referred pain in migraine [21, 22]. In this case, referred pain may account for patients' perception of pain in the front of the head, which is innervated by the ophthalmic division of the trigeminal nerve, and toward the back of the head, which is innervated by the greater occipital nerve [21, 23]. Animal models have increased our understanding of this phenomenon. Nociceptive afferent signals in nerves originating from the C2 spinal root and traveling via C fibers have been shown to reduce the threshold for activation and increase spontaneous firing of central neurons in mouse models [21].

Clinical evidence also implicates the GON, as blocking it leads to rapid relief of not only headache pain, but also other symptoms of migraine including neck pain, photophobia, and phonophobia [24]. One study found that of patients with migraine, 48% had involvement of the GON and could have their attacks aborted with targeted injection of anesthetics. These same patients could have attacks prevented for up

to 3 months with occipital neurectomy [25]. A case series exploring the efficacy of GON blockade with local anesthetics has shown reduction in headache pain and allodynia in GON's cutaneous distribution and the trigeminal distribution, furthering evidence of the functional link [10]. Another study explored this link by measuring the reactivity of the nociceptive blink reflex in patients without a history of primary headache disorder. After finding significant decrease in the reflex among these healthy patients undergoing GON blockade, the study postulated that afferents from the occipital nerve may have an excitatory effect on the trigeminal system, which can be inhibited by simple anesthetics [26]. Collectively, these studies show strong evidence that the GON plays a role in the development of chronic headache conditions like migraine. Alternative treatments that directly target the GON may decrease both the frequency and severity of migraine attacks while minimizing the incidence of abortive medication overuse. The remainder of this paper explores developments in occipital nerve stimulation as an alternative migraine treatment.

Occipital Nerve Stimulation

The mechanism of action of ONS is still under investigation; however, literature suggests that electrical stimulation of C1–C3 nerves, particularly the greater and lesser occipital nerves, reduces the activity of nociceptive fibers in the trigeminocervical complex resulting in pain relief, according to the "gate control" theory [27]. Gate control theory describes the mechanism by which painful sensation can be blunted or reduced by activating a non-painful sensation. The spinal cord holds the neurological "gate" that permits or prevents pain impulses from reaching the brain. The gate is opened when pain signals travel along tiny nerve fibers and closed when non-painful stimulation is applied to bigger fibers, preventing pain sensations from reaching the central nervous system [27].

Clinical Trials–Safety and Efficacy

A multicenter, randomized, single-blind phase-I clinical trial sponsored by Medtronic (ONSTIM, NCT00200109, Study 1 in summary table) sought to establish preliminary safety and efficacy data for ONS in the treatment of chronic migraine [28]. Participants were administered an occipital nerve block, and responders to the block were then randomly assigned to either an adjustable stimulation (AS), preset/sham stimulation (PS), or continued medical management (MM) group. Seventy-five out of 110 participants were assigned to a treatment group. After three months, participants were defined as responders to ONS if they achieved a 50% or greater reduction in the number of headache days per month, or a three point or greater reduction in average pain sensitivity compared to baseline. During the trial, no subject experienced an unanticipated treatment-related adverse event, although of the 51 subjects with implanted devices, 24% experienced lead migration. Responder rates were 39% in the AS group, 6% in the PS group, and 0% in the MM group. Preliminary safety and efficacy data from this trial were promising, prompting further investigation into ONS as a chronic migraine treatment [28, 29•].

In 2006, Boston Scientific Corporation initiated a randomized, double-blind phase-II study to evaluate the safety and efficacy of their PRECISION Implantable Stimulator for the treatment of migraine (PRISM US, NCT00286078, Study 2) [30••]. The PRECISION system had previously been approved by the FDA for use in spinal cord stimulation [31••]. Eligible participants (n = 125) were randomly assigned to a treatment group (n = 63) or control group (n = 62). The treatment group received active neurostimulation from the onset of the trial, while the control group received sham stimulation from the onset of the trial to 12 weeks post-activation. The control group was merged into the treatment group and received active stimulation indefinitely at 12 weeks post-activation. Long-term safety data were collected at a 12-year follow-up, although merging the control group into the treatment group at 12 weeks post-activation rendered this data unmeaningful. On average, subjects in the treatment group achieved a reduction in headache days/month of 5.5 (SD = 8.7), whereas the control group achieved a reduction of headache days/month of 3.9 (SD = 8.2). The results of the trial as they pertain to safety and efficacy are inconclusive, as the differences between treatment and control groups in reduction of headache frequency from baseline were not statistically significant. Boston Scientific later attempted two additional trials with the PRECISION system in 2008 and 2013 (PRISM UK, NCT00747812; OPTIMISE, NCT01775735), but both were terminated due to insufficient enrollment [31, 32]. The failure of these trials to yield conclusive results reflects more on the study design than the safety and efficacy of the treatment, given that the primary purpose of the trial was to safely carry out treatment on those enrolled, not to collect statistically sound data (30).

In a clinical trial conducted at the Pain Unit and Headache Center at Sacro Cuore Don Calabria Hospital in Negrar, Italy, 34 patients with a diagnosis of chronic migraine (CM) or medication overuse headache (MOH) were enrolled (NCT00407992, Study 3) [33, 34••]. After enrollment, participants' quality of life and headache-related disability were quantified by the Migraine Disability Assessment (MIDAS) and the SF-36 questionnaire, a general health-related quality-of-life questionnaire. MIDAS is a 5-question tool used to determine the severity of headache-related daily pain and

disability, which gauges the time lost from work, school, and social/family/leisure activities over the preceding 3 months due to headache, and the average severity of the headaches. A MIDAS score greater than 20 is classified as grade IV, or severe disability. This trial used the Numeric Rating Scale (NRS-11) to measure the headache intensity. After baselines were established, all participants underwent a trial period with temporary ONS. Following the trial period, 31 participants who were receptive to ONS went on with permanent implantation. Reception to the device was determined by a 50% decrease within 15–30 days in the number or severity of attacks. Ultimately, 30 participants were randomized (1:1) in either the On or Off arm of treatment. After one month, participants crossed over to the other arm of treatment or turned the device on when their headaches worsened. Quality of life, disability, and drug intake were quantified over a one-year follow-up. Headache intensity and frequency were significantly lower in the On arm than in the Off arm. Additionally, headache intensity decreased from the baseline to each follow-up visit in all patients with Stimulation On (median MIDAS A and B scores: baseline = 70 and 8; one-year follow-up = 14 and 5, $p < 0.001$). Patient quality of life improved significantly ($p < 0.05$) during the study. Triptans and nonsteroidal anti-inflammatory drug use decreased from baseline (20 and 25.5 doses/month) to each follow-up visit (3 and 2 doses/month at one year, $p < 0.001$) [33].

Incidence of adverse events was used to determine the safety of ONS. In this study, 2 patients (6%) had implantation-site infections, while 3 patients (10%) had lead migrations. In the majority of ONS trials, the most common adverse event aside from implantation-related pain was lead migration [35, 36]. A rationale suggested in this study for the low incidence of lead migration was the study's specific surgical technique for implanting the device [33]. The data from this trial give stronger support for the efficacy and safety of ONS as an anti-migraine treatment. Crossover assignment allowed each participant to receive the treatment at some point during the course of the study while maintaining the integrity of the controls. Results of a similar but longer-term study (7-year follow-up, Study 4) reinforce this data [37].

Another trial involved the Bion microstimulator and aimed to evaluate one-year outcomes post-implantation with a focus on implantation technique and stimulation amplitude optimization (NCT00205894, Study 5) [38]. The Bion microstimulator's small size allows a less invasive technique for implantation adjacent to the greater occipital nerve, which could decrease the number of adverse side effects in comparison with more invasive devices that utilize subcutaneous implantation in the occipital region. The study included 9 patients with medically refractory primary headache disorders [38]. Follow-up post-implant was conducted at 6 months to document stimulation parameters and maps, and one-year outcomes were quantified using MIDAS. Nine Bion microstimulators were implanted, with one patient stopping the use of the device before the one-year follow up. At the 6-month follow up, mean perception threshold, mean discomfort threshold, and paresthesia threshold were determined to be 0.47 mA, 6.8 mA, and 1.64 mA, respectively. Perception threshold is the lowest current amplitude that could elicit sensation, representing local tissue stimulation. Discomfort threshold is defined as the current amplitude where patients experience strong paresthesia and do not wish to increase the amplitude further. The stimulation range encompasses the perception threshold to discomfort threshold. Usage range was defined by the equation of discomfort threshold divided by perception threshold and represents the therapeutic stimulating window's relative size. Direct GON stimulation at a particular amplitude (termed the paresthesia threshold) was indicated when the patient noted sensations traveling toward the vertex of their head. During the study, the maximum stimulation amplitude tested was 10 mA.

At one year, 7 of the 8 patients acquired fair or better results in the reduction of disability with 5 patients rating greater than 90% reduction. Out of the 8 patients who completed the study, there was a mean decrease in the number of headache days at 28.5 (SD = 29.6). Headache severity score on average decreased by 0.88 (SD = 1.36). Usage of the stimulator ranged from 30 min every 2 weeks to 24 h/day, and recharging frequency ranged from 35 min/week to 4 h/day. This information was self-reported. No device-related complications, such as infection, migration, or erosion, were reported throughout the one-year duration of the study. A recent meta-analysis of adverse events in occipital nerve stimulation clinical trials showed that lead migration was the second most common device-related adverse event (preceded by implantation site pain) and that rates of these events are determined largely by implantation technique [36]. Promising results from the Bion microstimulator trial provide evidence that these adverse events can be minimized through optimization of surgical techniques.

Garcia-Ortega et al. report on the possibility of effective analgesia with the use paresthesia-free waveforms in ONS for CM and chronic cluster headache (CCH) (Study 6). ONS systems classically deliver constant stimulation via small current pulses to the nerves in a regular pattern. The regular pulsation pattern produces paresthesia in the scalp. This pattern is denoted as "tonic" stimulation (tONS). Effective pain relief has been traditionally thought to require paresthesia to be effective. Paresthesia-free pain relief is possible either through bursts of stimulation or stimulation at much higher frequencies [39]. In this study, 17 patients with CM or CCH were treated with paresthesia-free burst ONS (bONS) [40]. To determine the efficacy of the treatment, number of headache days per month and average intensity of the headaches were recorded for CM, while for CCH cluster attack frequency and intensity of the headaches were recorded. The

Table 1 Summary of Clinical Trials

Author (Year of Study)	Groups Studied and Intervention	Results and Findings	Conclusions
1. Saper JR et al. (ONSTIM Trial, 2011) [28]	Phase I, multicenter randomized, single (investigator) blind. Seventy-five participants with treatment-refractory chronic migraine were assigned to either an adjustable stimulation (AS), preset/sham stimulation (PS), or continued medical management (MM) group. Reduction in number of headache days/month and reduction in pain severity were assessed at a 3-month follow-up	Three-month responder rates were 39% in the AS group, 6% in the PS group, and 0% in the MM group. There were no unanticipated adverse events, but lead migration occurred in 24% of participants with an implanted stimulator	Preliminary data on safety and efficacy are promising, although no definitive conclusions can be drawn. Further study is warranted
2. Lipton R (PRISM US, 2016) (30)	Phase II, randomized, double-blind. Participants (n = 125) were randomly assigned to a treatment group (n = 63) or control group (n = 62). The treatment group received active neurostimulation from the onset of the trial, while the control group received sham stimulation from the onset of the trial to 12 weeks post-activation. The control group received real stimulation following the 12-week follow-up	Treatment group achieved on average a 5.5-day/month (SD = 8.7) reduction in migraine frequency, while the control group achieved a 3.9-day/month (SD = 8.2) reduction. Incidence of adverse events was comparable between treatment and control groups, but merging the control group into the treatment group after 12 weeks limits the data's usefulness	Results from this trial are inconclusive given the merging of treatment and control groups. Additional trials with more statistically sound design are necessary to draw conclusions
3. Serra and Marchioretto (2012) [33]	Open-label, randomized, crossover assignment trial. Thirty participants were randomized (1:1) in either the On or Off arm of treatment. After one month, participants crossed over to the other arm of treatment or turned the device on when their headaches worsened. Disability and headache intensity were quantified with the MIDAS, SF-36, and NRS-11 assessments	Headache intensity and frequency were significantly lower in the On arm than in the Off arm ($p < 0.05$). Quality of life significantly improved ($p < 0.05$) during the study. Triptans and nonsteroidal anti-inflammatory drug use fell dramatically from the baseline to each follow-up visit ($p < 0.001$)	Data from this trial support the safety and efficacy of ONS, although the lack of masking is a weakness. This study indicates that ONS may be helpful in reducing rates of triptan and NSAID use
4. Rodrigo D et al. (2017) [37]	Long-term, open-label, uncontrolled study. Following a ten-day trial, 35 responders to temporary treatment received a permanent ONS implant. Assessments included pain Visual Analogue Scale (VAS), number of migraine attacks/month, sleep quality, functionality in social and labor activities, and reduction in pain medication. The average follow-up time was 9.4 years	On average, VAS decreased by 4.9 ± 2.0 points. These results remained stable over the follow-up period. Five of the 35 permanently implanted patients with migraine attacks at baseline were free from these attacks at their last visits, whereas the pain severity decreased 3.8 ± 2.5 (VAS) in the remaining patients	The study indicates that ONS may be effective for long-term treatment of chronic migraine, although the uncontrolled open-label design limits the study

Table 1 (continued)

Author (Year of Study)	Groups Studied and Intervention	Results and Findings	Conclusions
5. Trentman TL et al. (2009) [38]	Open-label, uncontrolled study. Nine participants with medically refractory headache disorders received stimulator implants. Stimulation parameters (mean perception threshold, mean discomfort threshold, and paresthesia threshold) were mapped at a 6-month follow-up. Efficacy was assessed at a one-year follow-up and quantified through MIDAS. One participant discontinued use of the stimulator before the conclusion of the trial	Mean perception threshold, mean discomfort threshold, and paresthesia threshold were determined to be 0.47 mA, 6.8 mA, and 1.64 mA, respectively. At one year, 7 of the 8 patients acquired fair or better results in the reduction of disability with 5 patients rating greater than 90% reduction. There was a mean decrease in the number of headache days at 28.5 (SD = 29.6). Headache severity score on average decreased by 0.88 (SD = 1.36). No major adverse events were reported	ONS showed a clinically significant reduction in headache frequency and severity, although lack of control group precludes conclusions on statistical significance. Low rate of adverse events suggests possible improvements in safety
6. Garcia-Ortega R et al. (2019) [40]	Open-label, uncontrolled study. Seventeen participants with chronic migraine (n = 12) or chronic cluster headaches (n = 5) were enrolled. Patients were treated with paresthesia-free burst occipital nerve stimulation (bONS). For chronic migraine, number of headache days per month and average intensity of the headaches were recorded, while for chronic cluster headache, cluster attack frequency and intensity of the headaches were recorded	For chronic migraine, patients experienced on average a reduction of 10.2 headache days/month. For chronic cluster headache, cluster attack frequency was reduced by 92%, while intensity was reduced 42%, both representing a significant improvement from baseline. Two patients experienced complications (infection) that required explantation during the course of the study	The data from this study suggest that bONS can be effective in preventing primary headache pain; however, the study is limited, as it had no control group of traditional tONS treatment to compare with the experimental bONS group
7. Hann and Sharan (2013) [41]	Open-label, uncontrolled study. Fourteen patients with chronic migraine refractory to medical treatment were enrolled. After a 5-day trial, responders received permanent implants. Follow-ups were conducted every 3 to 6 months during the first year of treatment, then yearly thereafter	Of the 14 participants, 71% achieved improvement in headache severity and frequency and 50% were able to achieve both normal quality of life and resolution of associated migraine symptoms. Three of 14 participants had previously undergone ONS treatment without success but showed improvement in symptoms when SONS was added. Complications included lead migrations, infections, and discomfort sustained at supraorbital nerve stimulator electrodes	The study gives tentative, preliminary support to the safety and efficacy of dual stimulation. A larger comparative study is necessary to determine if dual stimulation is more effective than ONS alone

results of the study revealed a statistically significant reduction of 10.2 headache days/month in CM. In CCH, cluster attack frequency was reduced by 92%, while intensity was reduced by 42%. Significant improvement was reported from baseline; however, there was no control group of traditional tONS treatment to compare with the experimental bONS group. Future studies may involve a larger sample size and randomized double blind to provide a more accurate representation of this treatment's efficacy. Only 2 patients experienced complications (infection) that required explantation during the course of the study.

In the past decade, new innovations of neurostimulation duos have been on the frontier. Combining ONS and SONS for primary headache disorders was being tried to gain a better understanding and add additional evidence to the treatment method of neurostimulation. A sample of 14 CM patients who were refractory to medical treatments were enrolled in a dual stimulation (ONS and SONS) trial (Study 7) [41]. The trial began with a temporary 5-day period to test their responsiveness to the device. A responsive patient was defined as someone who experienced a $\geq 50\%$ pain reduction. Those who were responsive went on to have permanent stimulators implanted. Follow-up occurred the first few months post-implant, every 3–6 months within the first year, and then yearly follow-up thereafter. Follow-up period ranged from 3 to 60 months. During follow-up visits, patients' pain reduction, functional status, complications, and associated migraine symptoms were recorded. The results of this study support the effectiveness of dual neurostimulation. Within the sample size of 14 patients, 71% achieved improvement in headache severity and frequency and 50% were able to achieve both normal quality of life and resolution of associated migraine symptoms. Also, 3 out of the 14 patients previously were treated with ONS with differing levels of success. These patients then had additional SONS placement and were able to achieve a significant decrease in headache severity. Regarding the safety of this invasive device, complications included lead migrations, infections, and discomfort sustained at supraorbital nerve stimulator electrodes. A summary of the discussed clinical trials is given in Table 1.

Conclusion

Designing randomized double-blinded trials with sham control for implantable neurostimulators has proven somewhat difficult, for both practical and ethical reasons. Patients with occipital nerve stimulators will almost always feel paresthesia from stimulation, while sham stimulation will not elicit any sensation. Any attempts at masking will soon fail after the onset of treatment. Studies with crossover assignment mitigate this problem by having each subject serve as his or her own control. Further, sham surgeries are considered ethically unacceptable by many, as such a surgery exposes a patient to health risks without any possible benefit. These difficulties in study design may explain why there are currently no FDA-approved implantable occipital nerve stimulators for the treatment of migraine. While ONS is not approved specifically for migraine, existing clinical trial data do support the safety and efficacy of ONS for the treatment of migraine (33, 37, 38, 41). Further, general neurostimulation (including ONS) is approved by the FDA for the treatment of certain pain syndromes. Thus, ONS remains an evidence-supported off-label application of neurostimulation that is accessible for patients with intractable migraine.

Migraine, especially the chronic form, is a debilitating condition that causes profound negative effects on quality of life. Current medications prove effective for some patients but are not always successful and are prone to overuse. Furthermore, patients who overuse acute relief medications have a higher risk of their condition worsening. ONS has shown promise in clinical trials and could be recommended as a non-pharmacological alternative treatment for intractable migraine and other chronic headache conditions.

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Compliance with Ethical Standards

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• Of importance
•• Of major importance

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