**Neurostimulation for Neck Pain and Headache**

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**Abstract and Introduction**

**Abstract**

Patients with medically refractory headache disorders are a rare and challenging-to-treat group. The introduction of peripheral neurostimulation (PNS) has offered a new avenue of treatment for patients who are appropriate surgical candidates. The utility of PNS for headache management is actively debated. Preliminary reports suggested that 60–80% of patients with chronic headache who have failed maximum medical therapy respond to PNS. However, complications rates for PNS are high. Recent publication of 2 large randomized clinical trials with conflicting results has underscored the need for further research and careful patient counseling. In this review, we summarize the current evidence for PNS in treatment of chronic migraine, trigeminal autonomic cephalagias and occipital neuralgia, and other secondary headache disorders.

**Introduction**

Medically refractory headache is a rare, multicausal disabling condition that by definition is difficult to treat. Chronic forms of headache, in which there are daily or near-daily attacks, are particularly challenging. Medications used to abort headache can have intolerable side-effects, and frequent use of these drugs can result in medication-overuse headache. In lieu of medication, surgical treatments have been attempted with variable success.[1]

Peripheral neurostimulation (PNS) has been studied in several headache types as an alternative to destructive and more invasive procedures. Although PNS was initially studied in patients with occipital neuralgia (ON),[2] the past decade has seen expansion of the indications for PNS to include primary headache such as chronic migraine (CM) and trigeminal autonomic cephalagias (TAC). The literature on PNS has grown substantially and become more complex. Recent publication of 2 large randomized controlled trials (RCTs) for occipital nerve stimulation (ONS) with conflicting results highlights the active and controversial state of the field. Below, we comprehensively review the evidence to date PNS for CM, TAC, and ON, with emphasis on efficacy and adverse side-effects.

**Nomenclature**

The studies included for review were published over a period of nearly 20 years, during which the classification of headache types changed dramatically. The terminology used in these studies is mixed and can be confusing. Although the concept of chronic daily headache (CDH) predates the International Classification of Headache Disorders, the terms "chronic migraine" and "trigeminal autonomic cephalagias" were non-standard prior to the publication of the second edition (ICHD-2) in 2004.[3] In the migraine studies that were published before 2004, many authors use the Silberstein and Lipton classification of "transformed migraine (TM)," which denotes a syndrome of frequent headaches in a patient who either has a history of migraine, suffers concurrent or superimposed migraine, or who has a period of escalating headache frequency.[4] In contrast, "chronic migraine," introduced in ICHD-2, is a syndrome of migraine without aura on greater than 15 days per month, in a patient who does not have evidence of medication overuse. "CDH," which refers to a clinical syndrome of headaches for greater than 4 hours per day on greater than 15 days per month over a period of greater than 3 months, is not included in the ICHD-2, but can encompass both TM and CM. Studies of PNS in migraine published after 2004 adhere to the ICHD-2 definitions. For our purposes, the terms TM, CM, and CDH are treated synonymously. In the TAC literature, the terminology is consistent between studies. Each of the TAC studies included uses the ICHD-2 classification. The ON literature also has mixed terminology including cervicalgia and occipital headache and references publications other than the ICHD-2,[5–7] but all studies agree ON as a paroxysmal pain that occurs in the distribution of the greater or lesser occipital nerves.

**General Considerations**

Although the burden of disease is high, the total population of patients with medically refractory headache is small. The estimated combined prevalence of CM, chronic cluster headache (CCH), and intractable ON is less than 6%.[8,9] Of these, medically refractory cases are a minority. Therefore, the evidence on PNS for headache is frequently limited by small sample size, and case reports constitute the bulk of the literature. Patient selection criteria are poorly defined in many studies. Although all studies state that patients were implanted only after failure of medical management, there is no explicit standard for the duration or number or medications that qualify as a sufficient trial. No studies have rigorously examined which patient factors appear to predict success. Some studies purport that patients who respond to occipital nerve block (ONB) are more likely to have positive responses,[10] but there is clearly a population of patients who respond to PNS but are refractory to ONB.[11,12]

The efficacy of PNS in treatment of headache is difficult to study because of the subjective and often nebulous symptoms of headache, and head and neck pain in general. There are significant overlaps in presentation between different headache diagnoses, and multiple headache types often exist within the same patient. The natural history of headache, with fluctuating symptoms and periods of respite, can confound results. Furthermore, blinding is difficult because of the parasthesias that accompany effective stimulation. Outcome measures are not uniform between studies, making comparison difficult. Patients appear to have variable latency in responding to PNS ranging from days to weeks, and long-term follow up is necessary to determine the true efficacy of an implant. Lastly, there are no studies that compare PNS head to head against other invasive treatments for headache.

For the purposes of this paper, we will group studies into 3 broad categories according to headache type – CM, TAC, and ON. In nearly all studies, a reduction in either frequency or severity of headache of greater than 50% is considered a positive response, and we will adopt this convention when discussing outcomes.

**Mechanism of Action**

PNS was described in the writings of Scribonis Largus in 46 AD, when he recommended using the electric torpedo fish to treat headache.[1,13] Since then, our understanding how neurostimulation works on pain has evolved but is still incomplete. Currently, PNS is thought to modulate central pain processing by exploiting the anatomic and functional relationship of the peripheral sensory nerves of the head and neck to affect brainstem and higher cortical pain centers. Animal studies demonstrate that afferent nerves from the upper cervical spine synapse with dural and facial trigeminal inputs in the trigeminocervical complex in the brainstem.[14–16] This complex in turn interacts with higher-level neurons in the hypothalamus, periaqueductal gray (PAG), and thalamus for further processing of pain signals and reciprocal inhibition. Neurostimulation may affect this circuit in 2 complimentary ways. First, stimulation of afferent A-beta fibers induced by local electrical current blocks the nociceptive transmission of A-delta and group C fibers, as hypothesized in the "gate-control" theory of pain.[17] Second, stimulation of cervical afferents increases the activity of descending inhibitory pain pathways, particularly from the PAG. Positron emission tomography–computed tomography (PET-CT) studies in human subjects demonstrate increased activity of the PAG with spinal cord stimulation.[18] Thus, stimulation of peripheral nerves may prevent or abort headache that is centrally mediated.

**Operative Technique**

Permanent occipital nerve stimulator implantation was initially described by Weiner and Reed in 1999.[2] Patients who had failed 6 months of medical management of intractable ON were selected for implantation of permanent stimulators based on a positive response to a 5–7 trial of percutaneous ONS. In the operating room, patients were positioned in the lateral decubitus position or prone. Unilateral or bilateral electrodes were inserted in the region of the greater occipital nerves at the level of the C1 lamina. Both lateral submastoid and midline suboccipital incisions were used. The leads were anchored to the cervical fascia and then tunneled subcutaneously to a pulse generator placed in a subcutaneous pocket created in the flank or subclavicular region. C-arm fluoroscopy was used to confirm electrode location; however, patients were kept awake for the procedure in order to test for coverage of painful sites by parasthesias during temporary stimulation in the operating room.

Although the procedure remains largely unchanged, several groups have since modified the techniques described. First, not all groups require a successful trial of percutaneous simulation prior to implantation of permanent ONS. Some authors argue that a positive response to ONB is sufficient evidence to proceed with permanent implantation.19–21 Others are satisfied with an "on the table" test to check for adequate parasthesia coverage at the time of implantation.[22] Second, many groups advocate the use of paddle electrodes instead of cylindrical electrodes, arguing that paddle electrodes are less likely to migrate than cylindrical electrodes and may provide more uniform stimulation fields.[23] Lastly, some groups perform the entire procedure under general anesthesia, satisfied that fluoroscopy is adequate confirmation of lead placement.[24] Furthermore, intubation can guarantee airway protection in cases that often require complex patient positioning for lead placement and tunneling.

**Complications**

Permanent peripheral neurostimulators are associated with significant complication rates. Saper et al found that 71% of patients in the ONS for the treatment of intractable CM (ONSTIM) trial had a device related adverse event.[21] The most common complication is lead migration, with variably reported rates of 18–66%.[25,26] This is due to the mechanical stresses placed on the electrodes in the highly mobile neck region. The use of paddle electrodes and a shorter overall lead length may mitigate this problem somewhat.[22,27] Although the true rate of lead migration is unknown because of lack of routine imaging of implanted devices, lead migrations frequently result in loss of adequate coverage of parasthesias and return of pain. As a result, almost all lead migrations require reoperation. Infection is a serious concern and, when detected, often leads to explantation of the system. Recent series report infection rates of 6–20%,[19,21–25] with no apparent relationship to the duration or presence of temporary percutaneous stimulation trial. Other causes for explantation of neurostimulators include pain at the generator site, decreased or lack of efficacy, and intolerable stimulation side effects such as painful parasthesias. Because of these complications, 39% of patients had their device explanted at 1 year in a recent large trial.[25] Therefore, careful preoperative patient counseling and selection is essential. Further studies evaluating risk factors for failure are needed.

**CM**

CM (previously TM) or CDH, a disabling condition that affects up to 5% of the population, is the most common indication for implantation of ONS.[28] The utility of ONS in treatment of CM is under active investigation with conflicting data from small case series and more recently, 3 large industry-sponsored RCTs.

**Retrospective Case Series**

Popeney and Alo reported the first series of patients who underwent implantation of ONS for TM in 2003.[28] They reviewed 25 patients who previously met International Headache Society criteria for episodic migraine, but developed near daily headaches (greater than 15 days per month) that lasted greater than 4 hours. Inclusion criteria included a history of headache refractory to a 6-month trial of conventional management and normal magnetic resonance imaging. The mean migraine disability assessment questionnaire (MIDAS) score pre-implantation was 121, corresponding to severe disability. All patients responded to bilateral ONBs, and had a successful 5–7 day trial of percutaneous stimulation of bilateral occipital nerves. Intraoperative parasthesias were induced to confirm adequate electrode placement. At a mean follow up of 18 months, 88% of patients reported greater than 50% improvement in frequency or severity of headache. The mean MIDAS score was dramatically reduced to 15. Interestingly, 9 patients suffered either traumatic or spontaneous lead migrations and experienced loss of parasthesias that resulted in immediate relapse of symptoms.

Subsequently, several small case series have demonstrated that bilateral ONS is effective in alleviating headache in the majority of patients with medically refractory CM, albeit with significant rates of complications. Oh et al implanted paddle electrodes in 10 patients with TM and 10 patients with ON, and observed a response rate of 85% at 6 months with zero lead migrations.[22] They found that efficacy of ONS appeared to decrease over time, as the percentage of patient reporting excellent pain relief dropped from 85% to 70% during the course of the first 5 months of stimulation. Sixty percent of patients responded to ONS at mean follow up of 19.5 months in another study.[12] Unfortunately, all patients required lead revision at 3 years, and 42% of patients required battery revision at 2 years. Trentman et al implanted 4 patients suffering from CM with the Bion microstimulator (Boston Scientific, Valencia, CA, USA) without preoperative ONB or trial of stimulation and reported a response rate of 50% at 6-month follow up.[19] Recent publication of a 29-patient case series with long-term follow up of up to 102 months reported only 42% of patients with migraine regarded the procedure as successful, likely because of a high rate of complications.[26] Ultimately, 4 patients had their device explanted, and 66% of patients required at least 1 lead revision. ONS efficacy and patient satisfaction appear inversely related to duration of follow up. Whether this is due to tolerance effect or frequent complications is unclear. Reed et al's experience with combined occipital and supraorbital PNS in 7 CM patients suggest that dual coverage of painful areas may boost the effectiveness of stimulation. In their series, 6 patients reported greater than 90% improvement in pain, and 1 patient reported greater than 60% improvement at follow up of up to 35 months.[29]

**RCTs**

There are currently 3 industry-sponsored randomized prospective trials underway to evaluate ONS for CM.

The ONSTIM trial, sponsored by Medtronic, Inc. (Minneapolis, MN, USA), recently published 3-month follow up data that demonstrate modest efficacy of ONS for treatment of CM. Seventy-five subjects were randomized to either implantation with continuous stimulation, implantation with 1-minute daily stimulation, or medical management. Inclusion criteria for randomization included a positive response to ONB. At 3-month follow up, response rates were 39% for stimulation, 6% for sham stimulation, and 0% for medical management. The majority of patients had a device-related adverse event, with 26% rate of lead migration and 20% rate of wound infection.[21]

The precision implantable stimulator for migraine (PRISM) study, sponsored by Boston Scientific, Inc. (Natick, MA, USA), enrolled 125 patients who underwent a trial of percutaneous stimulation, then were implanted regardless of response, and randomized to either sham or bilateral stimulation. At the end of a 12-week blinded period, there was no significant difference between the 2 groups with respect to the primary end-point of change in headache frequency or severity from baseline.[10] Subgroup analysis showed that patients who initially responded to percutaneous stimulation had on average a decrease of 8.8 headache days per month vs 0.7 headache days in patients that did not respond to ONS (*P* < .001). At 2-year follow up, adverse events reported include device infection, non-target area sensory phenomena, and pain at the implant site.

Recently published data from the St. Jude (St. Paul, MN, USA)-sponsored trial corroborate the negative results of the PRISM study. This trial enrolled 157 patients across 15 centers and, extrapolating from the subgroup analysis of the PRISM trial, required a greater than 50% reduction in pain during trial stimulation for implantation. Patients were randomized 2:1 to active vs sham stimulation, with the primary outcome of greater than 50% reduction in headache at 12 weeks. There was no significant difference in primary outcome between the active and sham groups. Further analysis revealed that there was a significant reduction in the mean headache days between the active and sham groups (7.3 vs 4.2 days) and a significant difference between the 2 groups in the percentage of patients that rated headache relief as excellent or good (44% compared with 17.3%). Patients were subsequently followed for a 1-year open trial. At 1 year, 29% of patients had their device explanted. The most common complications were lead migration (18.6%) and pain at the implant site (21.5%).[25]

Serra and Marchioretto conducted the sole non-industry-sponsored prospective randomized cross-over trial. They randomized 30 patients who responded to trial stimulation 1:1 to 1 month of "on" or "off" stimulation, followed by cross-over of an equivalent period. Compared with patients in the "off" arm, patients who had active stimulation reported significant decreases in the number and severity of headache attacks. However, there were major flaws in the trial. No blinding was attempted, and there was a high rate of cross-over between the 2 arms (patients were allowed to switch their stimulators on if they experienced greater than 30% increase in headache). On average, patients switched from the sham to active arm in 5 days.[30]

The evidence to date for ONS in treatment of migraine is summarized in .

**Table 1.  Occipital Nerve Stimulators for Chronic Migraine**

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| --- | --- | --- | --- | --- | --- |
| **Study** | **Study Design** | **Trial/Electrode Type** | **Population** | **Results** | **Complications** |
| Popeney and Alo28 | Retrospective case series | 5–7-day trial stimulation with cylindrical electrodes‡ | 25 patients with medically intractable transformed migraine | Mean follow up of 18 months.  88% of patients reported >50% decrease in frequency or severity of headache. | 9 lead migrations (6 traumatic and 3 spontaneous) |
| Oh et al22 | Retrospective case series | 2-week extended trial stimulation with paddle electrodes‡, or "on the table" testing | 10 patients with occipital neuralgia and 10 patients with transformed migraine | At 1-month follow up, 85% of patients reported >90% pain reduction, and 15% patients reported>75% pain reduction.  At 6-month follow up, 70% of patients reported >90% pain reduction, 10% reported >75% pain reduction, and 5% of patients reported >50% pain reduction. 10% of patients were lost to follow up. | 2 infections, 1 treated with antibiotics, 1 requiring removal and replacement of electrode.  1 explantation due to new cervical pain.  1 explantation due to pain at the generator site.  No lead migrations with paddle electrodes. |
| Schwedt et al50 | Retrospective case series | 3–7-day trial stimulation with cylindrical electrodes‡ | 15 patients with medically intractable headache  Of these, 8 patients with chronic migraine | Mean follow up 19.5 months (range 5–42 months).  No subgroup analysis for migraine.  Overall, 52% reduction in headache at last follow up compared with baseline.  60% of patients reported >50% decrease in pain. | 8 patients (53%) had lead migration requiring surgery, all patients required lead revision for migration at 3 years after surgery  42% of patients required battery revision at 2-year follow up  No infections reported |
| Reed et al29 | Retrospective case series | 3–5-day trial stimulation period with cylindrical electrodes† | 7 patients with chronic migraine who underwent placement of combined supraorbital and occipital peripheral nerve stimulators | Follow up ranged from 1 to 35 months.  6 patients (86%) reported greater than 90% improvement in headache.  1 patient reported 60% improvement in headache. | 1 lead infection  1 lead migration with revision  1 titanium allergy leading to battery replacement |
| Trentman et al19 | Retrospective case series | No trial of occipital nerve block or stimulation.  A Bion (battery-powered, cylindrical microelectrode) device was used§ | 9 patients with medically refractory primary headache disorders.  4 patients presented with migraine. | At 6-month follow up, 2 migraine patients (50%) reported excellent responses; 1 reported fair response and 1 did not complete the study. | 1 patient dropped out of study because of stopping use of the stimulator due to amount of time required for recharging the Bion battery.  1 revision due to device malfunction.  1 explantation due to infection |
| Lipton et al10 | Prospective randomized controlled trial (PRISM) | Trial stimulation, followed by implantation of cylindrical electrodes§ regardless of response rate | 125 patients with medically refractory migraine randomized to stimulation vs sham stimulation | At 12-week follow up, no difference between the sham vs stimulation groups in the primary outcome of change in headache frequency or severity. Patients who responded to trial stimulation had a reduction of 8.8 headache days per month compared with 0.7 headache days per month in non-responders (*P* < .001) | At 2-year follow up adverse events reported included device infection, sensory phenomenon, and pain at the implant site. |
| Saper et al21 | Prospective randomized controlled trial (ONSTIM)  Industry sponsored | No trial stimulation. Positive response to occipital nerve block required for randomization.  Cylindrical electrodes implanted‡ | 75 patients with chronic migraine randomized 2:1:1 to ONS implantation with adjustable stimulation (AS), implantation with preset stimulation (PS) (1 minute per day), or medical management (MM) | 3-month follow-up data available.  39% of AS patients reported >50% decrease in headache days or a 3-point of greater reduction in overall pain intensity compared with baseline vs 6% in the PS group and 0% in the MM group.  Headache days, pain, and duration of headache were not statistically different between AS and control groups. | 26% of patients had lead migration or fracture  20% of patients had surgical site infection  Overall, 71% of patients had a device-related adverse event |
| Brewer et al26 | Retrospective case series. | 3–7-day trial stimulation with paddle electrodes‡ | 29 patients with medically intractable headache underwent trial of stimulation; 26 patients underwent permanent implantation.  12 patients diagnosed with chronic migraine | Follow up of up to 102 months.  42% of patients with migraine regarded the procedure as successful. | 4 explantations: 3 due to ineffectiveness, 1 due to infection.  13 lead revisions. 66% of patients required at least 1 lead revision. |
| Serra and Marchioretto30 | Prospective randomized cross-over study. | 15–30-day trial stimulation with paddle electrodes‡ | 30 patients with medically intractable chronic migraine and medication overuse headache.  Patients were randomized to on or off stimulation for 4 weeks, followed by cross-over period, then 12-month open-label period. | During periods of randomization, patients with stimulation had a median of 2.1–2.3 headache days per week compared with 6–6.3 headache days per week for patients who had no stimulation.  At 12-month follow up with open-label stimulation, the median MIDAS score decreased to 10 from 70 at baseline. | 2 explantations due to site infection.  3 lead migrations requiring revision. |
| Silberstein et al25 | Prospective randomized controlled trial  Industry sponsored | Trial stimulation period with cylindrical occipital electrodes† | 157 patients with chronic migraine randomized 2:1 to active vs sham stimulation over 12 weeks followed by open-label phase of 1 year.  Patients in both arms had pre-implantation temporary trials of stimulation | At 12 weeks, there was no difference between the 2 groups with regard to the primary outcome of >50% reduction in headache in mean daily visual analog scores. Headache days in stimulation group had decreased 7.3 days per month compared with 4.2 days in the control group (*P* = .015). 44% of active stimulation patients rated headache relief as excellent or good compared with 17.3% of the control group.  Compared with sham stimulation, the active group had more patients with greater than 30% reduction in headache, greater reduction in headache days, and lower migraine-related disability scores. | 21.5% of patients complained of pain at the implant site.  18.6% of patients had lead migration.  6.5% of patients had infection  4.7% of patients had lead fracture or device malfunction  6.5% of patients had unintended stimulation effects  There were no differences in complications rates between groups.  At 1 year, 46 (29%) patients had ONS explanted. |

†St. Jude Medical Neuromodulation (Plano, TX, USA).  
  
‡Medtronic Neuromodulation (Minneapolis, MN, USA).  
  
§Boston Scientific (Valencia, CA, USA).  
  
MIDAS = migraine disability assessment questionnaire; ONS = occipital nerve stimulation.

There is currently level 1b evidence from a single RCT that approximately one third of patients with CM will respond to ONS. However, 2 subsequent larger RCT have reported overall negative results (although there were trends suggesting improved headache control that did not reach significance). Rates of complications ranged from 43% to 71%, with lead migration as the most common indication for revision surgery.

**TAC**

TAC are a rare heterogeneous group of headache disorders that are characterized by unilateral pain in the trigeminal distribution, often with associated autonomic symptoms. The majority of patients with TAC respond readily to medical management (in fact, response to indomethacin is a diagnostic criteria for hemicrania continua [HC]). A small number of patients who are unresponsive to medications or have contraindications to non-steroidal anti-inflammatory drugs have been successfully treated with surgery. Deep brain stimulation (DBS) has proven effective in CCH[31] and HC; and microvascular decompression has been used to treat short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT).[32] ONS has been explored as an alternative to these more invasive procedures, particularly in patients who cannot tolerate general anesthesia or those who have failed intracranial procedures. The evidence for the usefulness of ONS in treating TAC is limited to case series with fewer than 20 patients, often with heterogeneous patient populations and a minority of TAC patients.

**CCH**

CCH is the most prevalent form of drug-resistant TAC. Approximately 50 patients with medically refractory CCH have undergone ONS implantation with generally positive results.

Schwedt et al first reported a single patient with CCH who responded to ONS in 2006.[33] Shortly thereafter, Magis et al published results for ONS in 8 patients with CCH and reported an 85.7% response rate at 15-month follow up. Although 6 patients had recurrent attacks after an initial period of respite, the weekly average number of attacks decreased from 13.4 to 2.8.[34] They subsequently published results for an additional 15 patients in 2011, with the longest mean follow up to date of 29 months.[27] Nine patients were pain free, and 3 had improvement of 89% or greater. Two patients did not respond or described only mild improvement. Four of these patients were able to reduce their dosage of prophylactic medication. Interestingly, several patients were further evaluated using PET-CT after implantation. Compared with normal controls, patients with CCH had hypermetabolic activity in the ipsilateral hypothalamus, midbrain, and ipsilateral lower pons.[35] All of these areas, with the exception of the hypothalamus, normalized when the ONS was turned on. This suggests that unlike DBS, ONS does not act at the level of the hypothalamus and may be a complimentary approach to pain management.

Other case series were less optimistic. Of 8 patients implanted with the Boston Scientific Bion microelectrode without a trial of stimulation, 5 patients had at least 20% reduction in headache.[11] Two years later, an expanded update with 6 additional patients reported that 43% of patients had greater than 40% improvement with ONS.[20] Rates of lead migration were substantially higher than earlier studies at 29%, likely because of use of small cylindrical electrodes rather than paddle electrodes. A subgroup analysis of 4 patients with CCH who were implanted with the Bion microelectrode for ONS in an earlier larger study reported a response rate of 50% at follow up of up to 67 months.[36] Another subgroup analysis of patients with primary headaches who underwent ONS with long-term follow up demonstrated a response rate of 60% at follow up of up to 102 months.[26] A prosective open-label multicenter French study recently reported a response rate of 85% at follow up of 14.6 months and zero lead migrations.[37]

In all studies, there was a variable delay in the onset of ONS efficacy ranging from several days to months after initiation of stimulation. Patients also experienced changes in the efficacy of ONS over time. Some patients reported increasing pain relief at up to 1 year, while others reported decreasing effectiveness. The effects of ONS appear highly individualized, with no clear explanation. An unexpected finding described by 2 different groups is that half of all patients develop contralateral attacks of either pain or ipsilateral autonomic paroxysms.[34,36] These were not treated because they were infrequent, and patients did not consider them disabling.

With regard to complications, infections were reported in 20–30% of patients, the majority of which were delayed superficial infections that were treated with antibiotics. Electrode migration or fracture as seen in 25–53% of patients. Approximately one fourth of patients had their device explanted or turned off within 2 years of implantation because of discomfort at the generator site, lack of efficacy, and infection.

There have been a few case reports that show efficacy for peripheral stimulation at other target sites in CCH. Supraorbital nerve stimulators were implanted in a Japanese patient whose attacks fully disappeared after 2 months of stimulation and remained absent at 12 months postoperatively.[38] Vagal nerve stimulation (VNS) has been shown to be helpful for 2 patients with CCH who were not operative candidates for DBS.[39] There is also a single case report of VNS augmenting a patient's response to DBS for CCH.[40]

**HC**

To date, only 10 patients with HC treated by ONS implantation have been described. Of these, 7 have reported at least 50% improvement after a mean follow up of approximately 1 year.[26,33,41] Burns et al conducted the largest prospective trial to date. They implanted 6 patients with HC and contraindications to indomethacin with the Bion microelectrode. The study design included 3 months of active stimulation, followed by 1 month of sham stimulation, and then an open trial of long-term active stimulation. The trial was not blinded. There were significant differences in pain control between active and sham stimulation. At a median follow up of 13.5 months, 4 patients reported 80–90% improvement by headache diary. One patient had a 30% improvement, and 1 patient had worsening of his pain by 20%. Response to stimulation was not predicted by response to nerve block.[41]

**SUNCT/Short-lasting Unilateral Headache Attacks With Autonomics Symptoms**

Lambru et al conducted an open-label trial for ONS in 9 patients with short-lasting unilateral headache attacks with autonomics symptoms (SUNA) and SUNCT. Preliminary results at 31-month follow up are encouraging: 4 patients reported complete resolution of symptoms, and 4 patients reported greater than 80% improvement in headache.[42,43] Complications included development of new HC as well as lead migration and erosion.

The evidence to date for ONS in treatment of TAC is summarized in . There is currently level IV evidence for the efficacy of ONS in treating TAC. Small retrospective case series report response rates of 60–87.5% in CCH. The evidence for supraorbital stimulation or VNS is anecdotal. ONS has also shown 70% efficacy for HC and 89% efficacy in SUNA/SUNCT in small case series. Complications are common, and revision rates range between 20% and 53%.

**Table 2.  Occipital Nerve Stimulators for Trigeminal Autonomic Cephalagias**

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| --- | --- | --- | --- | --- | --- |
| **Study** | **Study Design** | **Trial/Electrode Type** | **Population** | **Results** | **Complications** |
| Magis et al34 | Prospective open-label trial | 1–3 days of trial stimulation with paddle electrodes‡ | 8 patients with CCH | Mean follow up of 15 months.  Average weekly frequency of attacks reduced from 13.4 to 2.8.  Attacks recurred in 6 patients.  87.5% of patients reported improvement in quality of life. | 1 stimulator was switched off because of unbearable parasthesias and then explanted.  2 lead migrations, 1 requiring revision. |
| Schwedt et al50 | Retrospective case series | 5–7-day trial of stimulation with cylindrical electrodes‡ | 12 patients with chronic headache  3 patients with CCH  2 patients with HC | Mean follow up 19.5 months (range 5–42 months).  No subgroup analysis.  Overall, 52% reduction in headache at last follow up compared with baseline.  60% of patients reported >50% decrease in pain. | 53% patients had lead migration requiring surgery, all patients required lead revision for migration at 3 years after surgery  42% of patients required battery revision at 2 year follow up  No infections reported |
| Burns et al41 | Prospective cross-over study | No trial of occipital nerve block or stimulation.  A Bion (battery-powered, cylindrical microelectrode) device was used§  3 months of active stimulation followed by 1 month off, followed by long-term stimulation | 6 patients with HC who had contraindications to indomethacin therapy | Follow up of 6–21 months.  67% of patients reported >50% improvement of headache. 1 patient reported 30% improvement, and 1 patient reported worsening of pain.  5 patients reported worsening of headache during stimulation off period. | No major adverse events were reported. |
| Burns et al20 | Prospective open-label trial | No trial of stimulation.  Cylindrical electrodes‡ | 14 patients with CCH, 8 previously reported in Burns et al11 | Mean follow up of 17 months.  3 patients reported >90% improvement, 3 patients reported 40–60% improvement, and 4 patients 20–30% improvement. | 29% of patients required revision of electrodes  43% of patients required replacement of battery within the follow-up period |
| Trentman et al19 | Prospective open-label trial | No trial of occipital nerve block or stimulation.  A Bion§ (battery-powered, cylindrical microelectrode) device was used | 9 patients with medically refractory primary headache disorders.  5 patients with CCH. | At 6-month follow up, 3 cluster headache patients (60%) reported excellent response, 1 reported fair response, and 1 reported poor response. | 1 patient dropped out of study because of stopping use of the stimulator due to amount of time required for recharging the Bion battery.  1 revision due to device malfunction.  1 explantation due to infection |
| Magis et al27 | Prospective open-label trial | 3–7-day trial of stimulation with paddle electrodes‡ | 15 patients with CCH | Mean follow up of 36.8 months (range 11–64 months).  64% of patients are pain free at long-term follow up.  21% of patients reported >90% improvement in attach frequency.  14% of patients had little or no improvement. | 5 explantations (33%) – 3 due to infection, 2 due to discomfort at the battery site  2 patients found ONS-induced parasthesias unbearable.  1 electrode migration  64% of patients required battery replacement |
| Strand et al36 | Prospective open-label trial | No trial of occipital nerve block or stimulation.  A Bion§ (battery-powered, cylindrical microelectrode) device was used | 4 patients with CCH, previously reported in Trentman et al19 | 1 patient did not complete headache diary  At 12-month follow up, 2 patients had >50% reduction in headache  At 58- to 67-month follow up, 3 patients continued to use ONS with positive response. | 1 revision for battery malfunction |
| Fontaine et al37 | Multicenter prospective open-label trial | No uniform preoperative evaluation. Multiple electrodes used. | 13 patients with CCH | Mean follow up of 14.6 months.  11 patients (85%) reported >50% decrease in headache  3 patients did not require parasthesias to obtain therapeutic effect | 1 infection requiring explantation  1 infection treated with medical management |
| Brewer et al26 | Retrospective case series | 3–7 days of trial stimulation with cylindrical electrodes‡ | 29 patients with medically intractable headache underwent trial of stimulation; 26 patients underwent permanent implantation.  5 patients with CCH  2 with HC | Follow up of up to 102 months.  60% of CCH patients reported >50% improvement  50% of patients with hemicrania continua reported >50% improvement | 58% of patients underwent at least 1 lead revision.  3 explantations for ineffectiveness |
| Lambru et al43 | Prospective open-label trial | Trial not specified. Electrodes not specified | 9 patients with medically intractable SUNCT (6) and SUNA (3) | Median follow up of 31 months  4 patients became pain free  4 patients reported >80% improvement | New onset hemicrania continua  Lead migration  Electrode erosion  Muscle pain |

†St. Jude Medical Neuromodulation (Plano, TX, USA).  
  
‡Medtronic Neuromodulation (Minneapolis, MN, USA).  
  
§Boston Scientific (Valencia, CA, USA).  
  
CCH = chronic cluster headache; HC = hemicrania continua; ONS = occipital nerve stimulation; SUNA = short-lasting unilateral headache attacks with autonomics symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

**ON and Other Secondary Headache**

ON was the first headache syndrome treated with ONS. Since Weiner and Reed published their original series in 1999,[2] there have been multiple prospective trials and retrospective case series but no RCTs.

In contrast to trials examining ONS for migraine where trial stimulation is variably applied, all studies testing the effectiveness of ONS for ON use a positive response to percutaneous trial stimulation as part of the inclusion criteria for permanent implantation. Patients with ON appear more likely to respond to ONS than patients with primary headache disorders, but direct comparisons are difficult because there is an absence of commonly used standardized validated scales in the literature.

**Prospective Open-label Trials**

Three prospective open-label trials with short-term follow up have demonstrated the efficacy of ONS for ON. Oh et al recruited 10 patients with ON to undergo ONS. At 1 month, all patients reported greater than 75% reduction in pain.[22] When these patients were followed at 6 months, all patients reported greater than 50% reduction in pain, but the effectiveness of ONS appeared to have decreased over time. Two subsequent small trials with less than 10 patients supported these excellent outcomes. Six patients reported significant decreases in the visual analog scale and pain disability scores at 3-month follow up.[23] In a contemporary study, 4 patients had greater than 50% reduction in pain at follow up of 4–16 months.[44]

**Retrospective Case Series**

In retrospective case series with long-term follow up, the results for ONS and ON are less impressive. Rates of response to ONS range from 71% at 47-month follow up,[45] to 60% at 102-month follow up.[26,46,47] Complication rates remain high. Of the 18 patients implanted with ONS for ON reported in the literature who have detailed follow up, 5 patients (27%) have had their ONS explanted because of infection, loss of stimulation, or unrelated resolution of pain.[45,46]

**Other Headache Types**

Amin et al retrospectively reviewed PNS for supraorbital neuralgia in 10 patients. They found that headache scores were significantly reduced at 30-week follow up, and patients reported a 60% decrease in the number of days with greater than 50% pain relief. These patients had a high rate of lead migration and infection, likely because of thinner subcutaneous tissues in the supraorbital region.[48]

ONS has been also used to treat patients with medically refractory Chiari malformation type 1 headache, with 85% response rate at mean follow up of 23 months.[49]

The evidence to date for ONS in treatment of ON is summarized in . There is currently level IV evidence for ONS treatment of ON based on retrospective case series. In general, there is a lack of long-term follow up for these patients; response rates have ranged from 40% to 85%. ON appears to be the headache disorder that is most responsive to ONS. Complication rates can reach 30%.

**Table 3.  Occipital Nerve Stimulators for Occipital Neuralgia**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Study Design** | **Trial/Electrode Type** | **Population** | **Results** | **Complications** |
| Weiner and Reed2 | Retrospective case series | 5–7-day trial of stimulation with cylindrical electrodes‡/† | 13 patients with medically refractory ON | Follow up of 1.5–6 years.  92% patients reporting greater than 50% pain relief.  61.5% patients reported >75% pain relief. | 1 revision for lead migration.  1 explantation due to spontaneous symptom resolution |
| Oh et al22 | Prospective open-label series | 2-week trial stimulation period with paddle electrodes‡ | 10 patients with ON and 10 patients with transformed migraine | No subgroup analysis.  At 1-month follow up, 85% of patients reported >90% pain reduction, and 15% patients reported >75% pain reduction.  At 6-month follow up, 70% of patients reported >90% pain reduction, 10% reported >75% pain reduction, and 5% of patients reported >50% pain reduction. 10% of patients were lost to follow up. | 2 infections, 1 treated with antibiotics, 1 requiring removal and replacement of electrode.  1 explantation due to new cervical pain.  1 explantation due to pain at the generator site.  No lead migrations reported with paddle electrodes. |
| Kapural et al23 | Prospective open-label trial | 7–15-day trial of stimulation with cylindrical electrodes‡ | 6 patients with ON | At 3-month follow up, visual analog scale scores changed from 8.66 ± 1.0 at baseline to 2.5 ± 1.3 (*P* < .0001). Pain disability index scores improved from 49.8 ± 15.9 to 14.0 ± 7.4 (*P* < .0005). | No complications reported. |
| Rodrigo-Royo et al44 | Prospective open-label trial | 7-day to 1-month trial of simulation with cylindrical electrodes‡ | 4 patients with ON | Follow up of 4–16 months.  All patients reported >50% pain relief.  75% patients reported >90% pain relief. | No complications reported. |
| Johnstone et al45 | Retrospective case series | 7-day trial of stimulation with paddle electrodes‡ | 8 patients with medically refractory ON | Follow up of 6–47 months.  71% of patients had a reduction in the visual analog score. All patients had reduced medication usage. | 2 explantations; 1 due to infection of the paddle electrode, another due to infection of the generator. |
| Slavin et al46 | Retrospective case series | 4–10 day trial of stimulation with cylindrical electrodes‡/† | 10 patients with intractable ON | Mean follow up of 22 months.  70% of patients reported 60–90% pain relief. | 3 explantations for loss of stimulation, infection, and spontaneous resolution of pain. |
| Melvin et al47 | Retrospective case series | 4–10 day trial of stimulation with cylindrical electrodes† | 11 patients with C2-mediated ON | Follow up of 12 weeks.  55% of patients with excellent response  18% of patients with good response  Overall, 64% decrease in headache frequency | 1 loose connection  1 lead migration |
| Amin et al48 | Retrospective case series | 5–7-day trial of stimulation with cylindrical electrodes‡ | 10 patients with supraorbital neuralgia | Follow up of 30 weeks.  Headache scores reduced from 7.5 ± 0.4 to 3.5 ± 1.2 (*P* = .0047).  Narcotic intake was significantly reduced.  Percentage of days with >50% reduction in pain was 60%. | 3 patients (30%) required lead revision, 1 due to migration and 2 due to infection. |
| Vadivelu et al49 | Retrospective case series | Trial stimulation with electrodes‡ | 13 patients with Chiari malformation type I headache refractory to medical management | Mean follow up of 23 months.  85% of patients reported >50% pain relief. | 31% of patients required reoperation for device-related complications |
| Brewer et al26 | Retrospective case series | 3–7-day trial of stimulation with cylindrical electrodes‡ | 29 patients with medically intractable headache underwent trial stimulation; 26 patients underwent permanent implantation.  5 patients with ON | Follow up of up to 102 months.  2 patients with ON (40%) reported >50% improvement in symptoms.  1 patient had spontaneous resolutions of symptoms.  2 patients (40%) reported >30% improvement in headache. | 2 explanations. 1 due to spontaneous improvement of headache with move to higher altitude and 1 due to failure of ONS.  1 lead revision in these patients. |

ON = occipital neuralgia.

**Conclusion**

The use of PNS for treatment of medically refractory headache is an active area of investigation with promising preliminary results for certain headache populations such as TAC and ON where response rates range from 60% to 90% at long-term follow up. The efficacy of PNS for CM has not been definitively established despite 3 large RCTs. A larger question is whether for any patient the benefits of PNS outweigh the risks of a procedure that has a high rate of complications and high likelihood of reoperation with long-term use. Given the difficult patient population, and the refractory nature of the disease, implantation of PNS for medically resistant CDH is a reasonable option and may be preferred to other, more invasive procedures. Larger prospective randomized trials and detailed analysis of factors that predict success are needed to help select patients for PNS. There is also a scarcity of data on the costs of PNS in comparison of medical management or other surgeries. The need for effective treatment of medically refractory headache is high, and research efforts are ongoing.

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**Abbreviations**   
  
CCH chronic cluster headache; CDH chronic daily headache; CM chronic migraine; DBS deep brain stimulation; HC hemicrania continua; ICHD-2 International Classification of Headache Disorders 2nd edition; MIDAS migraine disability assessment questionnaire,ON occipital neuralgia,ONB occipital nerve block; ONS occipital nerve stimulation; ONSTIM occipital nerve stimulation for the treatment of intractable chronic migraine; PAG periaqueductal gray; PET-CT positron emission tomography-computed tomography; PNS peripheral neurostimulation; PRISM precision implantable stimulator for migraine; RCT randomized controlled trial; SUNCT short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; TAC trigeminal autonomic cephalagias; TM transformed migraine; VNS vagal nerve stimulation

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