Efficacy of Electrical Stimulation of the Occipital Nerve in Intractable Primary Headache Disorders: A Systematic Review with Meta-Analyses

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Aims: To determine the efficacy of occipital nerve stimulation (ONS) in reducing the intensity, duration, and frequency of medically intractable primary headaches. **Methods:** A systematic review was carried out by searching three electronic databases: the Cochrane Library, MEDLINE via PubMed, and Web of Science. Randomized controlled trials (RCTs) and case series were eligible for inclusion. RCTs were assessed for quality of evidence by using the Cochrane Risk of Bias and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tools. Descriptive statistics of reported outcomes in eligible studies are presented in tabular form. Meta-analyses of RCTs comparing ONS therapy to sham therapy in chronic migraine patients were conducted for the outcomes responder rate, headache frequency, and headache intensity. **Results:** Four RCTs, 1 follow-up study, and 19 case series met the inclusion criteria. The quality of the evidence was low, with all four RCTs assessed as having a high risk of bias and small sample size. Meta-analyses of three RCTs showed patients receiving ONS therapy had a significant reduction of 3 headache days per month (difference in means = −3.061; 95% confidence interval [CI] = −5.162 to −0.961; $P = .004$) and a significant reduction in Migraine Disability Assessment score (standardized difference in means [SDM] = −0.634; 95% CI = −0.933 to −0.335; $P < .001$) compared to sham (subthreshold) therapy. There were no statistically significant differences in reduction in pain intensity (SDM = −1.220; 95% CI = −2.489 to −0.049; $P = .060$) or in the number of responders (risk ratio [RR] = 1.581; 95% CI = 0.749 to 3.355; $P = .229$). **Conclusion:** ONS may be effective when compared to sham therapy, but the small number of RCTs and the heterogeneity of outcomes suggest further research in this field is needed. *J Oral Facial Pain Headache 2018;32:40–52. doi: 10.11607/ofph.1784*

Keywords: *chronic migraine, cluster headache, meta-analyses, occipital nerve stimulation, primary headache disorders*

Intractable primary headaches are disabling, debilitating, and difficult to treat. Traditionally, these disorders have been treated with medications to abort the migraine at onset (such as triptans) or with preventive medications taken prophylactically (such as beta-blockers [propranolol], anti-epileptic drugs [topiramate], or antidepressants [tricyclics]).[1–4] However, some individuals suffering from intractable primary headache disorders do not attain adequate relief from their symptoms by taking medications.[3] The continual use of these pain medications can also lead to medication overuse headaches (MOH), a comorbidity that must be clinically examined for and ruled out in chronic pain patients.

Researchers have sought alternative therapies to treat these patients, including acupuncture, acupressure, relaxation/biofeedback, and/or electrical stimulation. Peripheral nerve stimulation of the occipital nerve has been used for 40 years for treatment of chronic migraine since a case series experiment in humans in 1967,[5] although the use of neurostimulation for the treatment of headache or craniofacial pain is not currently approved by the Federal Drug Administration (FDA) in the United States of America. The case series by Weiner and Reed in 1999[6] on the use of percutaneous leads in the treatment of occipital neuralgia encouraged further clinical

studies using occipital nerve stimulation (ONS) for treatment of intractable primary headaches. According to Tepper in 2014:

> *Sometimes our best pills, well-placed injections, and lifestyle modifications are not enough, and headaches persist without sufficient relief. In such cases, battery-charged, electrical, or magnetic stimulators may be considered.*[7]

There are at least two stimulators in development for the treatment of intractable primary headaches that involve no surgery: noninvasive stimulation of the vagus nerve and transcranial magnetic stimulation.[7] Three stimulators need implantation of the device: sphenopalatine ganglion stimulation, hypothalamic deep brain stimulation (for intractable cluster headaches), and ONS, where a percutaneous lead is implanted at the level of C1 or C1 through C3 to stimulate the greater occipital nerve.[6,8–12] The lead can be implanted unilaterally or bilaterally and is connected to a pulse generator implanted into a subcutaneous pocket in the chest, abdomen, or back.[6,8–12] The exact mechanism of action of ONS is not completely understood. One theory, based on animal studies, has described ONS as having a modifying effect on the afferent impulses transmitted from the occipital nerve nexus (the C1–C3 spinal nerves) to the trigeminal brainstem subnucleus caudalis region and eventually to higher areas for processing.[13–15]

ONS is well developed and has been the focus of four recent randomized controlled trials (RCTs) for the treatment of chronic migraine patients.[9–12] A recent study on adverse events in the management of chronic migraine by ONS concludes that device characteristics and clinical skill and precision by the implanter are related to the number of adverse events.[16] Therefore, the aim of this systematic review was to determine the efficacy of ONS in reducing the intensity, duration, and frequency of medically intractable primary headaches.

Materials and Methods

The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[17] were followed in this systematic review.

Eligibility Criteria

Eligibility criteria were limited to clinical trials and case series on the efficacy of electrical stimulation of the occipital nerve in intractable primary headache disorders in reducing the intensity, duration, and/or frequency of pain compared to sham therapy. Reviews, systematic reviews, editorials, animal studies, conference proceedings, and guidelines were omitted. Articles not available in English were also excluded. Study participants were limited to adults over the age of 18 with intractable primary headache disorders (chronic migraine/transformed migraine, chronic cluster headache, occipital neuralgia, C2-mediated occipital headache, hemicrania continua, and posttraumatic headache) who were treated with electrical stimulation of the occipital nerve and evaluated for at least one of the primary or secondary outcomes listed below.

Primary Outcomes:

- Change in headache intensity (ie, visual analog scale [VAS] score) compared to baseline.[9,12]
- Number of responders to the intervention (the definition of responder varied among studies and included: A subject who experienced a 50% or greater reduction in number of headache days per month, a 3-point or greater reduction on a 0–10 VAS in average overall pain intensity compared with baseline,[9] a ≥ 50% decrease in intensity or severity of headache attacks,[8,10] or a 50% decrease in VAS pain intensity[11,12]).

Secondary Outcomes:

- Change in Migraine Disability Assessment (MIDAS) score[11]
- Posttreatment change in frequency of headache attacks (days/week or days/month)
- Change in treatment use of triptans
- Number of patients experiencing adverse events
- Number of patients who would recommend the device to other headache patients

Search Methods for Identification of Studies

The following electronic databases were searched.

- MEDLINE via PubMed was searched on February 19, 2015. The search strategy was: ("Electric Stimulation Therapy"[Mesh] OR (electric* stimulation occipital nerve)) AND (migraine OR headache* OR "Headache Disorders, Primary"[Mesh]) AND (occipital nerve) AND ((Clinical Trial[ptyp] OR systematic[sb] OR Review[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
- The Web of Science was searched on March 12, 2015 with the following strategy: (chronic headache* or migraine*) and (occipital nerve stimulation) and randomiz*
- The Cochrane Library was searched on March 12, 2015 as follows: (chronic headache OR migraine) AND (occipital nerve stimulation)

- An update of the search was conducted on June 6, 2016, at which point one new relevant reference was found. The reference sections of all included studies, as well as the reviews found throughout the search, were hand searched for eligible studies.

Data Collection and Analysis

Data Extraction and Management. Three reviewers (C.H., R.C., and J.D.) independently assessed the titles and abstracts of the references found through electronic searches and cross-referencing to determine eligibility. Any disagreements in the eligibility of an abstract were resolved by discussion with a fourth senior reviewer (R.E.) as the moderator. Full texts of the references were retrieved as needed to decide the inclusion or exclusion of eligible studies. The pertinent data from each study were obtained independently by using a specifically developed template table that included the characteristics of the study participants and the control groups (when applicable), interventions, and outcomes. All differences were resolved by discussion with a fourth reviewer (R.E.) as the moderator.

Assessment of Risk of Bias in RCTs. A risk of bias table was completed for each of the RCTs and crossover studies[9–12,18] independently by three reviewers (C.H., R.C., and J.D.). Any disagreements were discussed and resolved by discussion with a fourth reviewer (R.E.) as the moderator. The authors followed the approach described in the Cochrane Handbook for Systematic Reviews of Interventions.[19]

Assessment of Risk of Bias in Uncontrolled Studies. The evaluation of risk of bias in the uncontrolled studies and case series was based on a set of questions:

- Were the studies multi-center based?
- Were there clear study objectives/questions, explicit inclusion/exclusion criteria, and a specific recruitment time interval?
- Were the patients enrolled consecutively to control for selection bias?
- Were the outcomes clinically relevant?
- Was there a collection of prospective outcome data and adequate follow-up to account for attrition bias?

Each of these categories was appraised as "yes," "no," or "can't tell." A risk of bias table was then constructed for each study.

Statistical Analyses

Only RCTs or crossover studies reporting the same outcomes in a similar population (ie, chronic migraine patients) were included in the meta-analyses. Since authors reported pre- and posttreatment mean and standard deviation (SD) or mean change with SD, standardized differences in means (SDM) with 95% confidence intervals (CI) were reported for change in VAS headache intensity. Risk ratios (RR) with 95% CI were reported for number of responders (dichotomous variable). Cochran's (or Q) test[20] and the I^2 statistic[21] were used to test for statistical heterogeneity. When statistically significant heterogeneity (P value < .10) was found for the effect estimates, the results of the meta-analyses were based on the random-effects model; otherwise, the results were based on the fixed-effects model. All analyses were performed by using comprehensive meta-analysis software v2 (Biostat).

Levels of Evidence and Summary of the Review Findings

Assessment of quality of evidence and summary of the review findings were conducted following recommendations by the Cochrane Collaboration and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) group, with the software GRADE profiler (Grader).[19]

Results

Search Results

The initial search strategy yielded 138 references (including duplicates) from the electronic databases and 19 additional records identified through other sources (ie, scanning of reference sections of included studies and review articles). After duplicate entries were removed, 137 references were assessed independently by three review authors (C.H., R.C., and J.D.). Based on the abstracts and titles, there were 29 relevant manuscripts. Main reasons for exclusion were that the reference was a conference abstract (n = 1), case report (n = 2), editorial (n = 1), protocol for an RCT (n = 1), or review (n = 48); studied a different condition than intractable primary headache (n = 18) or used a different intervention than ONS (n = 30); measured different outcome(s) (n = 3); or had a different population (n = 4).

The full texts of all 29 manuscripts identified as eligible were searched and analyzed for inclusion independently by the three review authors, and 24 were deemed relevant for inclusion. Main reasons for rejection were that the reference was a case report (n = 1), review (n = 1), used a different intervention (n = 1), or studied a different condition (n = 2). Search results are shown in Fig 1.

Included Studies

A total of 24 studies relevant to ONS were included in this systematic review. Four of these reports

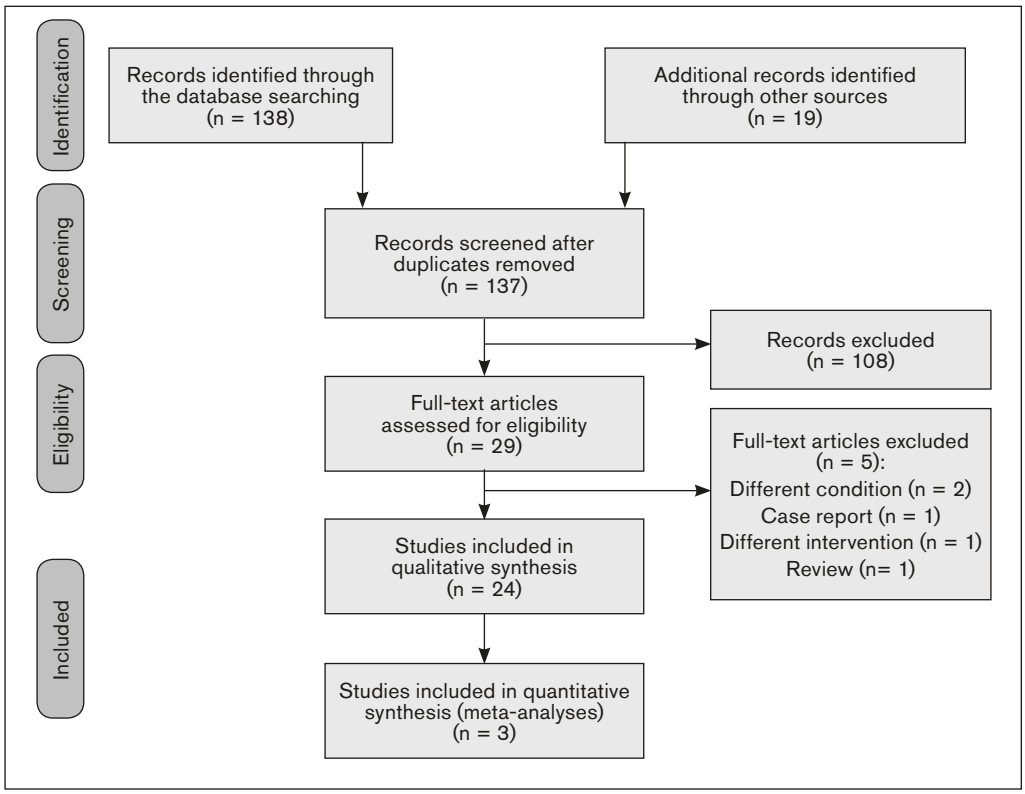

Fig 1 PRISMA[17] flow diagram.

were RCTs or crossover studies,[9–12] 1 was a long-term follow-up study of an RCT,[18] and 19 were either a prospective or a retrospective case series.[8,22–25,27–37,40–42] A summary of characteristics of included RCTs and crossover studies is presented in Table 1.

RCTs and Crossover Studies. Two studies were randomized crossover trials,[10,12] two were RCTs,[9,11] and one[18] was a follow-up of Silberstein et al.[11] Three studies[9,11,12] investigated ONS therapy in chronic refractory migraine patients, and one included chronic migraine (15%) and MOH patients (85%).[10] Four studies compared ONS active stimulation to sham (subthreshold) stimulation[9,11,12] or stimulation off.[10] Patients were prescreened for inclusion in the studies if they were positive responders to both occipital nerve blocks and a trial period of peripheral occipital nerve stimulation.

There were differences in the ONS device, as well as in the number and placement of the leads. Two studies[9,10] used a percutaneous quadripolar lead and a Synergy Versitrel stimulator (Medtronic). Two studies[11,12] utilized leads and stimulators from one manufacturer (St Jude Medical), but one[11] applied unilateral or bilateral leads based on individual pain patterns and used the Genesis stimulator, whereas another[12] applied bilateral leads on each study participant and used the Octrode stimulator.

Case Series. The 19 included case series studied the effect of ONS in the following diagnostic categories (demonstrating the inherent heterogeneity with medically refractory headache patients): occipital neuralgia,[22–24]transformed migraine,[8,23] chronic cluster headache,[25–32] hemicrania continua,[27,33] chronic migraine,[25,27,34] posttraumatic headache,[27] and generalized occipital headache mediated from C-1-2.[22,35] Chronic migraine was diagnosed according to the International Headache Society (IHS) 2004 criteria,[43] and chronic headaches, occipital neuralgia, and posttraumatic headaches were diagnosed clinically.

Risk of Bias in RCTs and Crossover Studies

Table 2 and Fig 2 show the results of the risk of bias assessment for the included RCTs and crossover studies.[9–12] All studies were at overall high risk of bias.

Random Sequence Generation. Three studies were at low risk of bias in this domain,[9,11,12] as they described their method of random sequence generation (ie, using computerized software,[11] applying MATLAB's rand algorithm,[12] or using a central randomization process provided and managed by a third party).[9] The method of randomization of patients in one study[10] was not explicitly stated, and the risk of bias is therefore unclear.

Table 1 Characteristics of Included RCTs and Crossover Studies

Study	Year; country; sample size	Interventions (no. of patients)	Summary of inclusion criteria[a]	Study type	Risk of bias
Saper et al[9]	2010; USA, Canada, UK; N = 75	ONS (28) Sham therapy (17) Medically managed (17) Ancillary group (8)	1. Diagnosis of CM headache as defined by the 2004 IHS criteria: Migraine headache occurring on average ≥ 15 days/month for more than 3 months in absence of medication overuse and not attributed to another disorder. 2. Refractory, as determined by failure to respond to or intolerance to an adequate trial of preventive medications from at least two different classes of drugs. 3. Pain located between C3 level and vertex. 4. Pain may be unilateral or bilateral and may include pain in frontal, temporal, or retro-orbital region or into neck/shoulder location. 7. Onset of migraine headache occurred before age 50 years. 8. Current acute and prophylactic headache medication regimens have been stabilized for 4 weeks prior to preliminary enrollment visit. 9. Response to a temporary, short-acting anesthetic block to the occipital distribution was positive. 10. Subject is age 18 years or older and has signed informed consent form, is available for follow-up, and willing and able to use electronic daily questionnaire equipment. 12. Female subject of childbearing potential has negative pregnancy test at confirmation of enrollment visit, is not nursing, and agrees to use adequate birth control methods for duration of study.	RCT	High
Serra and Marchioretto[10]	2012; Italy; N = 29	Crossover ONS: On ONS: Off	1. Diagnosis of CM or MOH and fulfilled the following inclusion criteria: ▪ Refractoriness to at least two prophylactic treatments or intolerable side effects due to these treatments ▪ No ongoing prophylactic treatments at the beginning or during the study ▪ Age ≥ 18 years ▪ Ability and willingness to participate in the study ▪ Written informed consent signed 2. In addition, MOH patients underwent a period of at least 2 months of drug withdrawal before the ONS trial. Baseline assessment was performed at the end of this period for these patients to avoid interference with the assessment of stimulation outcomes.	Crossover	High
Silberstein et al[11]	2012; USA; N = 157	ONS (105) Control (52)	Patient diagnosed with CM headache with the following diagnostic criteria: a) Headaches ≥ 15 days/month for > 3 months b) Headaches meet the 2004 IHS criteria for migraine without aura (1.1), migraine with aura (1.2), or probable migraine (1.6) on > 50% of the headache days. c) Not attributable to another disorder. d) Patients have tried at least two migraine-specific acute medications, and migraine symptoms were found to be refractory. e) Patients have tried at least two different classes of prophylactic medications, and migraine symptoms were found to be refractory. f) VAS score of ≥ 6 cm on a 10-cm line. g) Headache pain is posterior head pain or pain originating in the cervical region. h) Only patients who underwent a successful trial received implantation of the permanent system.	RCT	High
Slotty et al[12]	2015; Germany; N = 8	Crossover Effective stimulation Subthreshold stimulation No stimulation	Migraine patients treated with ONS were asked to participate in the study. To reduce potential effects of impedance changes, only patients reporting stable and significant (> 30%) pain relief for at least 3 months postoperative were included. Patients fulfilled the 2004 IHS criteria for chronic migraine. Further inclusion criteria: Age ≥ 18 years; stable medication; written informed consent	Crossover	High

[a]Please refer to original articles for full lists of inclusion criteria. IHS = International Headache Society (2004 criteria[43]); CM = chronic migraine; MOH = medication overuse headache.

Table 2 Summary of Risk of Bias for Eligible RCTs and Crossover Studies

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other potential bias	Overall bias
Saper et al[9]	–	–	?	–	–	+	+
Serra and Marchioretto[10]	?	+	+	?	–	+	+
Silberstein et al[11]; Dodick et al[18] (follow-up)	–	–	?	?	–	+	+
Slotty et al[12']	–	–	+	–	–	+	+

+ = high risk; – = low risk; ? = unclear risk.

Allocation concealment was reported in three of the studies,[9,11,12] as both patients and providers were blinded to the results of the randomization through the use of sealed envelopes (low risk). One study[10] lacked details as to participants or study personnel knowing treatment assignments; therefore, its overall risk of bias for allocation concealment was high.

Blinding. Two studies[9,11] were deemed at unclear risk of bias for blinding, as the researchers did attempt to keep patients, health personnel, and outcome assessors blinded to therapy and results, but no mention as to the nature of blinding was involved in the data analyses. The other studies[10,12] were at high risk for blinding since the study design did not allow for blinding of patients, as they could control the stimulation levels or switch the stimulator on/off.

Incomplete Outcome Data. Two studies adequately reported outcome data and were assessed as being at low risk for bias in this domain.[9,12] Two studies[10,11] demonstrated an unclear risk of bias for incomplete outcome data, as nonresponding patients were allowed to exit the studies.

Selective Reporting. All four RCTs and crossover studies[9–12] showed complete reporting on stated outcomes and were assessed at low risk of bias for this domain.

Other Potential Sources of Bias. All four included RCTs demonstrated high risk of bias from other potential sources due to patients being able to continue with medications throughout the studies and having the ability to alter stimulation levels without supervision. There was no mention of other comorbid conditions (ie, diabetes, other body pain areas, traumas to head/neck areas, structural abnormalities of the neck area, arthritis, etc) that could have an effect on the diagnosis or patient response to ONS. There was a stated conflict of interest in one study,[12] as two authors were consultants for or received grants from St Jude Medical, the manufacturer of the ONS system employed in the study. One study[11] showed a high risk of bias, as two of the authors who assisted in analyzing the data were sponsored by St Jude Medical, and another study[9] disclosed that one author was sponsored by Medtronic, the manufacturer of the ONS device used in their study. In addition, one study[10] allowed participants concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans and also allowed randomized patients to adjust their own stimulation.

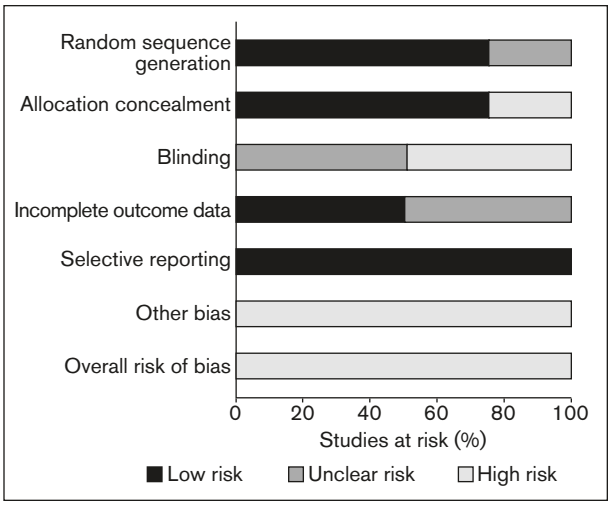

Fig 2 Graph of risk of bias for included RCTs and crossover studies.[9–12]

Risk of Bias in Case Series

All case series were assessed as at overall high risk of bias (Table 3).

Meta-Analyses for Chronic Migraine

Of the four included RCTs/crossover studies, three[9,11,12] reported pain outcomes in a similar fashion and could be included in the meta-analyses.

Responder Rate. Two studies[9,11] provided the intent-to-treat responder rate (ie, percentage of subjects who achieved a 50% or greater reduction in number of headache days per month with no increase in average headache duration[11] or a 3-point or greater reduction in average overall pain intensity compared with baseline[9]). No heterogeneity was found between those two studies (Q test $P = .168$; $I^2 = 47\%$). With the fixed-effects model, there was no significant difference in the number of responders to ONS therapy compared to the patients receiving sham therapy ($P = .229$; Fig 3).

Table 3 Summary of Risk of Bias for Eligible Case Series

Reference	Multi center	Clear study objectives	Explicit inclusion/ exclusion criteria	Specified recruitment time	Consecutive enrollment	Clinically relevant outcomes	Prospective outcome data collection	High follow-up rates	Overall risk of bias
Burns et al[31]	No	Yes	Yes	?	?	Yes	No	Yes	High
Burns et al[33]	No	Yes	Yes	No	?	Yes	Yes	Yes	High
Burns et al[32]	No	Yes	?	Yes	Yes	Yes	No	Yes	High
Fontaine et al[36]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	High
Johnstone and Sundaraj[40]	No	Yes	Yes	Yes	?	Yes	Yes	No	High
Kapural et al[24]	No	?	?	?	?	Yes	Yes	Yes	High
Magis et al[29]	?	Yes	Yes	Yes	?	No	Yes	Yes	High
Magis et al[30]	Yes	Yes	Yes	Yes	?	Yes	Yes	Yes	High
Matharu et al[34]	Yes	Yes	No	?	?	Yes	Yes	Yes	High
Melvin et al[35]	?	Yes	Yes	?	No	Yes	Yes	Yes	High
Mueller et al[37]	No	Yes	No	Yes	No	Yes	Yes	Yes	High
Mueller et al[25]	No	Yes	No	?	?	Yes	Yes	Yes	High
Oh et al[23]	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	High
Popeney and Aló[8]	No	Yes	Yes	?	Yes	Yes	Yes	Yes	High
Schwedt et al[27]	No	Yes	Yes	?	?	Yes	Yes	Yes	High
Slavin et al[41]	No	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Strand et al[28]	No	Yes	Yes	?	?	Yes	Yes	No	High
Trentman et al[42]	?	Yes	Yes	?	?	Yes	Yes	Yes	High
Weiner and Reed[22]	No	Yes	?	?	?	Yes	Yes	Yes	High

Yes = low risk; no = high risk; ? = unclear risk.

Reduction in Headache Days per Month. Two studies[9,11] provided the reduction in number of headache days per month on average compared with baseline. No heterogeneity was found (Q test $P = .943$; $I^2 = 0\%$). Patients receiving ONS therapy had 3 less headache days per month than patients receiving sham therapy, and this difference was statistically significant ($P = .004$; Fig 4).

Reduction in Headache Intensity. Two studies[9,12] reported the average reduction in headache intensity (VAS) with treatment. Significant heterogeneity was found (Q test $P = .057$; $I^2 = 72\%$). Patients receiving ONS therapy had a nonsignificant reduction on the VAS compared to patients receiving sham therapy ($P = .060$; Fig 5).

Reduction in MIDAS Score. Two studies[9,11] reported the reduction in MIDAS score compared with baseline. No heterogeneity was found (Q test $P = .465$; $I^2 = 0\%$). Patients receiving ONS therapy had a significantly improved MIDAS score ($P < .001$; Fig 6).

Results of the Case Series

Chronic Migraine. The summary of outcomes for included case series with chronic migraine patients[8,23,25,34] is presented in Table 4. A majority of these patients were female (89.1%) with an average age of 42.7 years and were followed an average of 12 months post–ONS implantation. The percent of responders as defined in the Methods sections ranged from 88%[8] to 100%[23,25,34] with ONS, with a decrease in pain intensity of −39%[8] to −87.5%.[34] Patients receiving ONS treatment also demonstrated a decrease in number of headache days per week, with a reported decrease of −26%[25] to −50%.[8] Also, patients in some studies[8,23,25,34] were able to decrease their migraine abortive medication (ie, triptan) use significantly with ONS (66%[25] to 100%[8,34] of the patients used less triptans, and in one study patients decreased their triptan use by −90%[23]). Adverse events in the ONS group were frequent (50% to 90% of the patients had at least one adverse event).

Cluster Headache. Eight case series were reviewed regarding ONS therapy and cluster headache[25,26,28–32,36] (Table 5). In these studies, 76% of the participants were male with an average age of 44 years and an average follow-up period of 18.5 months. Patient responder rates ranged from 20%[26] to 92%,[25] and the decrease in attack frequency ranged from −40%[25] to −95%[30] with ONS. Patients also reported an overall decrease in attack intensity of −17%[30] to −60%,[31] and between 38%[31] and 75%[29] of the cluster headache patients used less triptans

Study	Statistics				RR and 95% CI
	RR	Lower limit	Upper limit	*P* value	
Saper et al[9]	5.667	0.797	40.298	.083	
Silberstein et al[11]	1.273	0.568	2.855	.557	
Overall	1.581	0.749	3.335	.229	

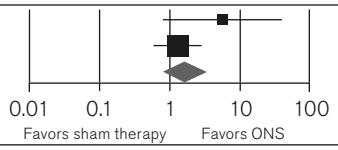

Fig 3 Results of meta-analysis for ONS compared to sham therapy for the outcome responder rate. RR = risk ratio; CI = confidence interval.

Study	Statistics				DM and 95% CI
	DM	Lower limit	Upper limit	*P* value	
Saper et al[9]	−2.900	−7.786	1.986	.245	
Silberstein et al[11]	−3.098	−5.424	0.771	.009	
Overall	−3.061	−5.162	0.961	.004	

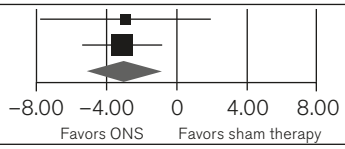

Fig 4 Results of meta-analysis for ONS compared to sham therapy for the outcome reduction in headache days per month. DM = difference in means; CI = confidence interval.

Study	Statistics				SDM and 95% CI
	SDM	Lower limit	Upper limit	*P* value	
Saper et al[9]	−0.667	−1.297	−0.037	.038	
Silberstein et al[12]	−1.978	−3.174	−0.782	.001	
Overall	−1.220	−2.489	0.049	.060	

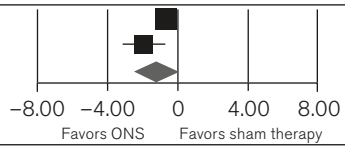

Fig 5 Results of meta-analysis for ONS compared to sham therapy for the outcome reduction in headache intensity on a visual analog scale. SDM = standardized difference in means; CI = confidence interval.

Study	Statistics				SDM and 95% CI
	SDM	Lower limit	Upper limit	*P* value	
Saper et al[9]	−0.844	−1.483	−0.205	.010	
Silberstein et al[11]	−0.575	−0.913	−0.236	.001	
Overall	−0.634	−0.933	−0.335	.000	

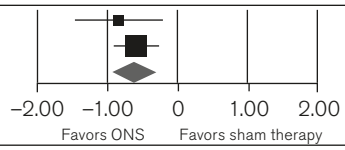

Fig 6 Results of meta-analysis for ONS compared to sham therapy for the outcome reduction in Migraine Disability Assessment score. SDM = standardized difference in means; CI = confidence interval.

with ONS. With these positive responses, 66%[30] to 100%[26] of case series patients would recommend an ONS device to other patients with cluster headache (Table 5).

Other Headache Disorders. Three case series reported ONS therapy on occipital neuralgia,[22–24] one reported on C2-mediated occipital headache,[35] one reported on hemicrania continua,[33] and one[27] reported on ONS therapy with a mixed pool of patients diagnosed with either hemicrania continua, posttraumatic headache, chronic migraine, or cluster headache (Table 6). The results of these studies utilizing ONS therapy with mixed chronic headache conditions also show positive therapeutic results. From 55%[35] to 100%[24] of patients improved at least 50%. Also, patients reported a decrease in headache pain intensity from −34%[27] to −71%[24] with ONS. The decrease in percent of headache attacks per week was reported in one case series as −29%.[27] Four case series[22–24,35] reported that patients were able to decrease or eliminate their use of triptans with ONS therapy, and three[23,33,35] reported that 83% to 100% of study participants would recommend ONS therapy to other headache sufferers (Table 6).

Table 4 Summary of Outcomes in Chronic Migraine/Transformed Migraine (CM/TM)

Study/study design	Headache category	No. of patients randomized/completed study	Mean age (y)	Mean follow-up (range)
Saper et al[9]/RCT	CM	Randomized: N = 75 (ONS: 28; Sham: 17; MM: 17; Ancillary: 8) Completed: N = 66 (13 M, 53 F)	43 ± 10.6	3 mo
Serra and Marchioretto[10]/crossover	CM (85% MOH)	Randomized: N = 30 Completed: N = 29(34% M, 76% F)	46 ± 11(26–66)	12 mo
Silberstein et al[11]/RCT	CM	N = 157 ONS: 24 M, 81 F Control: 9 M, 43 F	ONS: 45.0 + 11.3 Control: 44.6 + 10.3	3 mo
Dodick et al[18]/RCT follow-up	CM	ITT: N = 157 ONS: 24 M, 81 F Controls: 9 M, 43 F	ONS: 45.0 ± 11.3 Controls: 44.6 ± 10.3	52 wk
Slotty et al[12]/crossover	CM	N = 8	–	21 d
Matharu et al[34]/case series	CM/TM	N = 8 (1 M, 7 F)	44 (32–53)	18 mo (7–36)
Mueller et al[25]/case series	CM/TM	N = 3 (1 M, 2 F)	30	7 mo (5–12)
Oh et al[23]/case series	CM/TM	N = 10 (0 M, 10 F)	51.7 (41–83)	6 mo
Popeney and Alo[8]/case series	CM/TM	N = 25 (3 M, 22 F)	45 (31–65)	18.3 mo (9–36)

[a]A responder was defined as a subject who achieved a 50% or greater reduction in number of headache days per month, a 3-point or greater reduction in average overall pain intensity compared with baseline,[9] or a ≥ 50% decrease in intensity or severity of headache attacks.[8,10–12,23,25,34] M = male; F = female; MOH = medication overuse headache; MM = medically managed; ONS = occipital nerve stimulation; ITT = intent-to-treat; PP = per-protocol; VAS = visual analog scale.

Table 5 Summary of Outcomes in Chronic Cluster Headache (CH)

Study	No. of patients	Mean age (range) or ± SD, y	Mean follow-up (range), mo	Patients improved > 50%,[a] n/total (%)	CH attack frequency (%)	CH attack intensity (%)	Decrease in triptans use	Would recommend the device, n/total (%)
Burns et al[31]	8 (7 M, 1 F)	46 (32–58)	20 (6–27)	3/8 (37.5)	–	–60	38% used less	7/8 (88)
Burns et al[32]	14 (10 M, 4 F)	44 (31–58)	17.5 (4–35)	5/14 (36)	–	–37	57% used less or no use	11/14 (79)
Fontaine et al[36]	13 (8 M, 5 F)	44.6 + 11.6	14.6 (3–34)	10/13 (77)	–68	–49	62% used less	12/13 (92)
Magis et al[29]	8 (7 M, 1 F)	45.3	15.1 (3–22)	6/8 (75)	–79	–44	6/8 (75%)	7/8 (88)
Magis et al[30]	15 (14 M, 1 F)	47.6 + 11.5	36.6 (11–64)	11/15 (73)	–95	–17	4/15 (26%)	10/15 (66)
Mueller et al[26]	10 (8 M, 2 F)	39 (18–54)	12 (3–18)	2/10 (20)	–50	–29	7/10 (70%)	10/10 (100)
Mueller et al[25]	24 (17 M, 7 F)	30	20 (5–47)	22/24 (92)	–40	–37.5	–40%	22/27 (82)
Strand et al[28]	4 (2 M, 2 F)	(44–66)	12 (0–12)	2/4 (50)	–61	2/4 patients reported –60	–	–

All studies are case series.
[a]Responders were defined as patients who reported an overall estimate of improvement in CH of at least 50%[29–32,36] or had a ≥ 50% decrease in intensity, frequency, or severity of headache attacks.[25,26,28]

Adverse Effects

Therapy with ONS is not without complications. The number of adverse events with ONS therapy reported in included studies for chronic migraine is shown in Table 4, and the adverse events for other headache disorders are shown in Table 6. Generally, reported adverse events were treated, and patients continued with ONS therapy.

Levels of Evidence and Summary of the Review Findings (GRADE)

The level of evidence for all outcomes reported in this review was low due to a high risk of bias for all included studies, the small number of studies reporting each outcome (n = 2 for each), and the small sample sizes of the included studies (total number of participants in subgroup analysis below 400) (Table 7).

Percent of responders[a]	Percent change in pain intensity on VAS	Percent change in frequency of headache days	Percent change in triptans use	Adverse events in ONS group
ITT: ONS: 33; Sham: 6; MM: 0 PP: ONS: 39; Sham: 6 ; MM: 0	–	ONS: –27 Sham: –8.8 MM: –4.4 Ancillary: –39.9	–	71%
97	–25 to –33	–62 to –67	–85	17%
ONS: 17.1 Control: 13.5 (*P* = .55)	ONS: –42 Control: –19 (*P* = .001)	ONS: –27.2 Control: –14.9 (*P* = .008)	–	ONS: 73 events/105 patients Controls: 34 events/52 patients
ITT: 47.8	ITT: –49.5	ITT: –31 PP: –32	–	70%
–	ONS: –76 Sham: –31 (*P* = .0003)	–	–	None reported
100	–87.5%	–	100% used less	4 events/8 patients
100	–	–26	2/3 used less	–
100	–	–	–90.1%	9 events/10 patients
88	–39	–50	100% used less	10 events/25 patients

Table 6 Summary of Outcomes in Other Headache Disorders

Study	Headache type	No. of patients	Mean age (range), y	Mean follow-up (range), mo	Percent of patients improved > 50%[a] (n/total)	Percent change in pain intensity (0–10)	Percent change in attack frequency	Triptans use	Adverse events	Percent who would recommend device (n/total)
Kapural et al[24]	ON	6 (4 M, 2 F)	51.8 (40–72)	3	100 (6/6)	–71	–	3/6 never 3/6 less	–	–
Oh et al[23]	ON	10 (7 M, 3 F)	50.2 (32–75)	6	95–100	–	–	80% did not use at last follow-up	–	90 (9/10)
Weiner and Reed[22]	ON	13 (5 M, 8 F)	51.4 (26–72)	26.3 (18–72)	92 (12/13)	–	–	92% used little or none	3/13	–
Melvin et al[35]	C2-mediated occipital headache	11 (2 M, 9 F)	47.3 (36–65)	3	73	–67	–	91% used less	2/11 (18%)	100 (11/11)
Burns et al[33]	HC	6 (2 M, 4 F)	53.1 (37–64)	13.5 (6–21)	66 (4/6)	–49	–	–	4/6	83 (5/6)
Schwedt et al[27]	HC/ posttraumatic headache/CM/ CH	15 (3 M, 12 F)	39 (21–52)	19.5 (5–42)	60 (9/15)	–34	–29	–	9/15 surgical revision at 1 y	–

All studies are case series.

[a]Percent of patients with > 50% pain relief (good or excellent relief) calculated based on data presented by the authors.[22–24,27,33,35]

[b]Pain intensity was rated on a 0–10 visual analog scale. ON = occipital neuralgia; HC = hemicrania continua.

Discussion

This systematic review with meta-analyses has shown that there is favorable but low-quality evidence to support the use of ONS for decreasing the intensity and frequency of headache pain associated with intractable primary headaches. These results are similar to the findings by Chen et al.[38]

Cluster Headache

No RCTs on cluster headaches were found in the literature search (possibly due to the rarity of this condition), so the present authors decided to report data from case series. Overall, 66% to 100% of case series patients would recommend an ONS device to other patients with cluster headache. Although these rates are high, these data should be interpreted with

Table 7 Summary of Quality of Evidence Findings (GRADE)[19] ONS Compared to Sham Therapy for Intractable Primary Headache Disorders

Outcomes	No. of participants (no. of studies); follow-up	Quality of the evidence	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with sham therapy	Risk difference with ONS (95% CI)
Responder rate	207 (2); 3 mo	Low[a,b] due to risk of bias, imprecision	RR 1.581 (0.749 to 3.335)	Study population 116 per 1,000	67 more responders per 1,000 (from 29 fewer to 271 more)
Reduction in headache days	201 (2)	Low[a,b] due to risk of bias, imprecision			Mean reduction in headache days in ONS treatment was 3.061 days lower (5.162 to 0.961 lower) than with sham
Reduction in headache intensity on VAS	60 (2); 3–12 wk	Low[a,b] due to risk of bias, imprecision			Mean reduction in headache intensity in ONS group was 1.220 standard deviations lower (2.489 lower to 0.049 higher) than with sham
Reduction in MIDAS score	201 (2); 3 mo	Low[a,b] due to risk of bias, imprecision			Mean reduction in MIDAS score in the ONS group was 0.634 standard deviations lower (0.933 to 0.335 lower) than with sham

GRADE Working Group grades of evidence: High quality = Further research is very unlikely to change the level of confidence in the estimate of effect; Moderate quality = Further research is likely to have an important impact on the level of confidence in the estimate of effect and may change the estimate; Low quality = Further research is very likely to have an important impact on the level of confidence in the estimate of effect and is likely to change the estimate; Very low quality = Review authors are very uncertain about the estimate.

[a]Both studies at high risk of bias.

[b]Only two studies reporting this outcome; small sample size (total number of participants < 400).

RR = risk ratio; CI = confidence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; MIDAS = Migraine Disability Assessment Score.

caution, as there was no control group in these case series and the results might therefore be biased due to the placebo effect. Another possible confounder might be the psychosocial profiles of primary chronic or intractable headache patients.

Other Headache Disorders. The lack of RCTs on other headache disorders led to a review of case series on other headaches, including occipital neuralgia,[23] C2-mediated occipital headache,[35] and hemicrania continua.[33] Between 83% and 100% of patients with these disorders would recommend ONS therapy to those with similar conditions. Again, these data must be interpreted with caution due to the placebo effect.

Overall Completeness and Applicability of Evidence

Three main databases (MEDLINE through PubMed, Cochrane, and Web of Science) were searched in this systematic review. Other popular databases, such as EMBASE, were not available to the reviewers. Included studies and reviews were hand searched for eligible studies. The results of this systematic review are applicable to patients who are nonresponders or poor responders to conventional pharmacologic therapy for their headaches. None of the included studies reported on ONS as first-line therapy. Patients' headaches were classified according to the IHS 2004 criteria[43] for each distinct chronic headache classification. In addition, patients included in these studies suffered from a marked disability in their daily function. Patients were pre-screened for inclusion in the studies if they were positive responders to both occipital nerve blocks and a trial period of peripheral occipital nerve stimulation.

Quality of the Evidence

Only four of the reports were RCTs or crossover studies, and one additional study reported on data at the 1-year follow-up.[18] The evidence as presented in the four RCTs is biased due to a host of issues, notwithstanding the conflict of interest that exists due to researchers being compensated by the manufacturers of the neurostimulators. Therefore, because all RCTs and case series had overall high risk of bias and imprecision, the overall quality of the evidence was low.

MOH is a prominent disorder in chronic pain patients, yet only two studies made any attempt to account for this disorder.[8,10] Most of the studies acknowledged that the patients were taking or had taken various medications for their chronic pain. The lack of accounting for this disorder could also be a major bias in these studies.

Heterogeneity

The included studies had various differences that caused heterogeneity. Two of the main differences were the type/manufacturer of the implantable pulse generator and the number of leads placed (unilateral vs bilateral). Study designs and application of the stimulation also varied. Two studies[9,11] were RCTs utilizing a set range of stimulation parameters throughout the trial. One study[12] was a blinded crossover clinical trial that cycled patients through three different stimulation parameters: effective stimulation, subthreshold stim-

ulation, and no stimulation. Finally, one study[10] was a prospective, randomized crossover study in which the patients had the stimulation either on or off.

Agreements and Disagreements with Other Studies or Reviews

Based on the analysis of the included RCTs[9–12,18] and case series[8,22–25,27–37,40–42] referenced in this systematic review, ONS seems to have a role in the treatment of refractory headaches, although the quality of evidence is low. The authors agree with prior publications[9–11] that studies with better designs are needed to reduce bias and provide a clearer picture of the role of ONS in refractory headaches. Studies designed to identify which headache types are most responsive to neurostimulation and the patient profile best suited for this treatment are required to improve clinical outcomes with ONS.

Implications for Research

The biggest problem in the study design for this topic is blinding, which is difficult if not impossible, as there is no placebo equivalent for the paresthesia that accompanies stimulation.[39] In addition, further research to elucidate the mechanisms of action of ONS will assist in the effort to better determine the match-up of specific headache type to specific patient type best suited for this approach. High-quality diaries of medication use or inpatient studies are needed to control for medication usage, as it is a possible confounder. Lastly, hardware issues (eg, lead migration or dislodgement location of the pulse generator and battery design to reduce battery failure) must be addressed.

Conclusions

ONS therapy should be considered for pharmacophobic patients or headache patients who fail to respond to medications, injections, and lifestyle modifications. Patients should be informed about the low quality of evidence available to support the use of ONS. This will enable the patient to make an informed decision and also understand the limitations of this therapy. In addition, patients should also be informed about the benefits and side effects of ONS. Lastly, careful case selection on the part of the clinician is essential to avoid potential therapeutic failures.

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