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Long-Term Outcome in Occipital Nerve Stimulation Patients With Medically Intractable Primary Headache Disorders

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Introduction: Occipital nerve stimulation (ONS) may provide relief for refractory headache disorders. However, scant data exist regarding long-term ONS outcomes.

Methods: The methods used were retrospective review of the medical records of all (nonindustry study) patients who were trialed and implanted with occipital nerve stimulator systems at our institution, followed by a phone interview. Up to three attempts were made to contact each patient, and those who were contacted were given the opportunity to participate in a brief phone interview regarding their ONS experience. Data for analysis were gleaned from both the phone interview and the patient's medical records.

Results: Twenty-nine patients underwent a trial of ONS during the 8.5-year study period. Three patients did not go on to permanent implant, 12 could not be contacted, and 14 participated in the phone interview. Based upon the phone interview (if the patient was contacted) or chart review, ONS was deemed successful in five of the 12 migraine, four of the five cluster headache, and five of the eight miscellaneous headache patients, and therapy was documented as long as 102 months. In one of the 26 patients, success of ONS could not be determined. Among patients deemed to have successful outcomes, headache frequency decreased by 18%, severity by 27%, and migraine disability score by 50%. Fifty-eight percent of patients required at least one lead revision.

Discussion: These results, although limited by their retrospective nature, suggest that ONS can be effective long term despite technical challenges. The number of patients within each headache subtype was insufficient to draw conclusions regarding the differential effect of ONS.

Conclusions: Randomized controlled long-term studies in specific, intractable, primary headache disorders are indicated.

Keywords: Cluster headache, headache, migraine, occipital nerve stimulation, peripheral nerve stimulation

Conflict of Interest: Within the past three years, Drs. Trentman, Zimmerman, Dodick, and Vargas have received research support from St Jude-Neuromodulation and Medtronic, Inc. Dr. Dodick has provided consulting services within the past three years for Medtronic, Inc. and Boston Scientific Corporation. In the remote past (greater than three years), Drs. Trentman and Zimmerman provided consulting services for Advanced Bionics Corporation, now Boston Scientific Neuromodulation.

INTRODUCTION

Refractory headache disorders affect approximately 4% of the population worldwide and result in severe pain, debilitation, and limitation of lifestyle (1–3). Occipital nerve stimulation (ONS) was introduced in 1999 as a therapeutic option that may provide relief for patients unresponsive to medical therapy (4).

As reported in several small studies, electrical stimulation has been applied to the occipital nerve in the management of a variety of headache disorders including migraine, hemicrania continua, posttraumatic headache, and cluster headache (5–14). Although the use of spinal cord stimulation equipment to stimulate occipital nerves represents off-label use of the technology, there is a growing body of literature regarding ONS including technical aspects of the procedure, hardware, amperage, results, and complications (15). The mechanism of ONS is not fully elucidated,

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but imaging studies (both functional magnetic resonance imaging and positron emission tomography) suggest that ONS has central effects (16,17).

Scant data are available regarding long-term outcome of ONS for medically intractable headache disorders. Existing research on the efficacy of ONS is limited in both sample size and follow-up duration. We previously reported outcome data up to 42-month duration on 15 patients treated with ONS (8); the current study expands that data including additional patient implants. The objective of this study was to provide data on long-term success of ONS in medically intractable headache disorders. Outcome measures include success of ONS as deemed by the investigators and patient, headache day frequency, disability, pain severity, duration of ONS treatment from the date of permanent implant to the time of the phone interview (or the most recent clinic visit if the patient could not be contacted), number of lead revisions, and willingness of the patient to repeat the procedure.

These results will hopefully add to the understanding of ONS and its potential as a long-term treatment modality for medically intractable headache disorders.

METHODS

The institutional review board gave approval for both a chart review and phone survey. We retrospectively reviewed the medical records of all patients who were trialed with occipital nerve stimulator systems at our institution. Patients who participated in industry sponsored trials were excluded. Medical records obtained from the Department of Neurology and the Division of Pain Medicine provided patient diagnosis, previous treatments, and indication for ONS trial. All patients were evaluated by a neurologist with expertise in headache medicine and diagnosed according to the criteria of the International Classification of Headache Disorders I (prior to 2004) and II (18).

In each case before permanent implant, a three- to seven-day trial of ONS was performed by placing leads subcutaneously in the occipital region. If the patient reported 50% or greater reduction in pain intensity or headache frequency, the permanent device was implanted within several weeks. Unilateral headache patients underwent unilateral stimulation vs. bilateral stimulation for bilateral headache. As previously described, both midline and retromastoid approaches were used for lead placement combined with infraclavicular, buttock, and low abdominal implantable pulse generator sites (15,19).

Duration of ONS treatment was calculated as the months between implant and the date of the phone call or the most recent clinic visit if the patient could not be contacted. Operative notes provided data for trial procedure, permanent implantation, revision surgery, and explantation as applicable.

Next, a standardized phone survey was conducted to determine the long-term efficacy of ONS (Fig. 1). Up to three attempts were made to contact each patient, and those who were contacted were given the opportunity to participate in a brief phone interview regarding their ONS experience. The survey included questions regarding overall benefit and patient willingness to undergo the procedure again. Overall benefit was determined by asking patients to rate the overall effectiveness of ONS on a percentage scale. If the patient could not be contacted, overall benefit was judged from verbiage in the medical record at the most recent clinic visit. Where possible, the investigators also made their own assessment of the success of ONS. Success was defined as at least 50% overall benefit as reported by the patient in the phone interview or verbiage in the most recent clinic visit suggesting significant improvement, such as "excellent pain relief" or "complete pain relief."

About how long has it been since your stimulator was inserted?

On how many days in the last 3 months did you have a headache?

(If a headache lasted more than 1 day, count each day.) _____

On a scale of 0–10, on average how painful were these headaches?

(where 0 = no pain at all and 10 = pain as bad as it can be.) _____

Overall, how effective has the stimulator been for your headaches (0–100%)?

Knowing what you know now, would you have an occipital nerve stimulator placed again?

Figure 1. Phone survey questions.

The patients also were asked questions from the migraine disability assessment score (MIDAS) questionnaire (20). Frequency of headaches was measured by patient reported headache days during the previous three months. Intensity of headaches was a patient rating from 0 (no pain) to 10 (worst possible pain) during the previous three months. These results were compared with baseline values as found in the medical record to calculate the percentage change in frequency, intensity, and MIDAS. If the patient could not be contacted, MIDAS, frequency, and headache intensity data were gleaned from the medical record where possible. Therefore, data for analysis were gleaned from both the phone interview and the patient's medical records.

The data were summarized where applicable using descriptive statistics.

RESULTS

Twenty-nine patients underwent a trial of ONS during the study period, which covered 8.5 years (2002–2011). Of the 29 patients, three patients did not undergo permanent implantation: two patients experienced inadequate benefit during their trial to justify permanent implantation and one patient had a successful trial but did not proceed to permanent implantation due to financial constraint. Two patients are now deceased of unrelated causes. Of the 26 patients who underwent permanent implant, phone contact was made with 14, and all agreed to participate in the survey (Fig. 2).

Two patients (one migraine and one occipital neuralgia) reported spontaneous resolution of pain unrelated to ONS therapy. One had her ONS explanted while the other has stopped using his device. Two patients (one migraine and one posttraumatic headache) reported no benefit from permanent implantation despite a successful trial. Both were explanted after a short duration and would not repeat the therapy. An additional migraine patient (now deceased) received therapy for only one month before explantation for ineffectiveness.

There were a total of 25 lead revision procedures in the 916 months of ONS therapy, not including explantations. Fifteen of the 26 patients (58%) underwent at least one lead revision.

Table 1 summarizes outcome for 12 patients (all female) with a primary diagnosis of migraine, including the number of migraine preventative (non-narcotic) medications that had been tried before ONS implant, ±onabotulinum toxin A. The duration of ONS treatment ranged from 1 to 70 months. Five of the patients were con-

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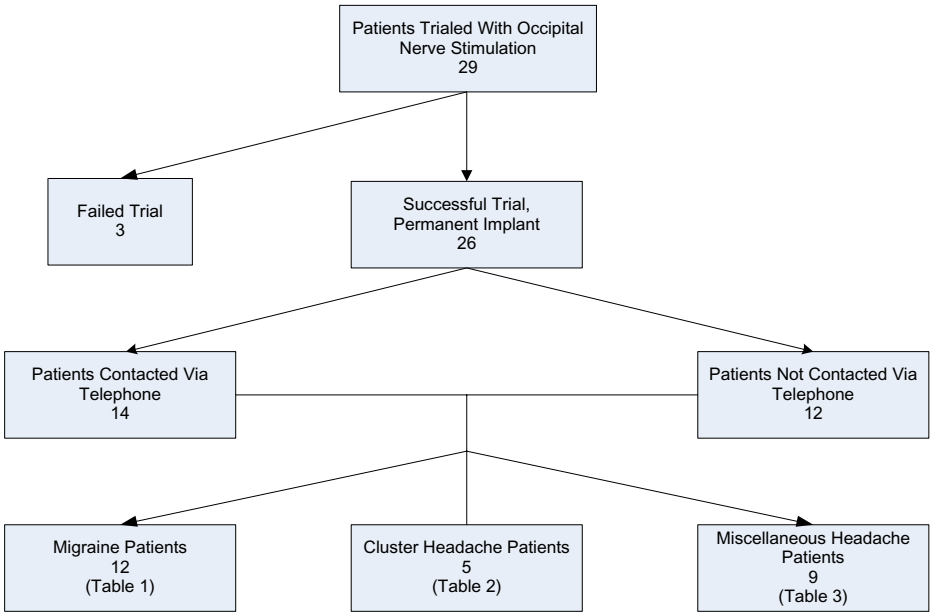

Figure 2. Patient flow diagram.

Table 1. Long-Term Outcome of Occipital Nerve Stimulation in Migraine Patients.

Patient/contact via phone?	Diagnosis	No. of migraine preventatives tried before ONS implant	Duration of implant (months)	Lead revision procedures	Overall benefit per patient or medical record	Would the patient repeat?	ONS deemed successful by investigator?	Notes
31 F/Yes	MI	6 + OTA	70	1	95%	Yes	Yes	
42 F/Yes	MI	19 + OTA	16	1	75%	Yes	Yes	Awaiting revision for lead migration
37 F/Yes	MI	15	69	0	85%	Yes	Yes	
42 F/Yes	MI	10 + OTA	62	2	40%	Yes	No	Does not help pain, just other symptoms (nausea and photophobia)
47 F/No	MI	8	19	0	"Complete"	Unknown	Yes	Unable to contact efficacious until explanted for infection
33 F/No	MI	10 + OTA	59	4	"Excellent"	Unknown	Yes	Now deceased of unrelated causes
40 F/Yes	MI	8	Unknown	1	Pain resolved spontaneously	No	No	Explanted at outside institution, patient could not recall date
34 F/Yes	MI	19	1	0	Not effective	No	No	Explanted after one month
60 F/No	MI, HC, ON	7	41	2	Not effective	Unknown	No	
34 F/No	MI	8 + OTA	27	0	Not effective	Unknown	No	
50 F/No	MI, ON	9 + OTA	9	1	Not effective	Unknown	No	
28 F/No	MI	8 + OTA	1	1	Not effective	Unknown	No	Explanted, now deceased of unrelated causes
40 (9) years			374	13 revisions		5/12 (42%) success		

Success ≥ 50% benefit per patient or verbiage in the medical record suggesting significant improvement. Age presented as mean (standard deviation). Duration of implant, from time of implant to time of phone call or most recent clinical note.
F, female; OTA, onabotulinum toxin A; HC, hemicrania continua; MI, migraine; ON, occipital neuralgia; ONS, occipital nerve stimulation.

tacted via phone; four of the five stated that they would repeat the procedure. Based on patient phone response or statements in the medical records, the investigators considered ONS to be successful in five of the 12 (42%) patients. One patient with only 40% overall benefit (who stated that she would repeat the procedure) was not deemed a success by our criteria, although she also noted a 60% decrease in headache intensity.

Table 2 summarizes outcome for five patients with chronic cluster headache. The duration of ONS treatment ranged from 5 to 102 months. Two of the five were contacted via phone; the investigators considered ONS to be successful in four of the five (80%) patients.

Table 3 summarizes outcome in a heterogeneous group of nine chronic headache sufferers, including posttraumatic, occipital neuralgia, and hemicrania continua. Duration of ONS therapy ranged from 9 to 90 months. In five of the eight (63%) patients, the investigators deemed ONS successful; the remaining nine patient experienced spontaneous resolution of his headache and so the impact of ONS could not be assessed.

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Table 2. Long-Term Outcome of Occipital Nerve Stimulation in Cluster Headache Patients.

Patient/contact via phone?	Diagnosis	Duration of implant (months)	Lead revision procedures	Overall benefit per patient or medical record	Would the patient repeat?	ONS deemed successful by investigator?	Notes
45 F/Yes	CL	42	1	70%	Yes	Yes	
53 M/Yes	CL	102	1	50%	Yes	Yes	
57 F/No	CL	9	1	"8 out of 10 improvement"	Unknown	Yes	Efficacious until battery depleted; insurance denied coverage for battery replacement
57 F/No	CL	5	0	Not effective	Unknown	No	
59 M/No	CL	5	0	"Doing very well"	Unknown	Yes	
54 (5.6) years		163	3 revisions			4/5 (80%) success	

Age presented as mean (standard deviation). Success ≥ 50% benefit per patient or verbiage in the medical record suggesting significant improvement. Duration of implant, from time of permanent implant to time of phone call or last clinic visit.
F, female, M, male; CL, cluster headache; ONS, occipital nerve stimulation.

Table 3. Long-Term Outcome of Occipital Nerve Stimulation Patients With Miscellaneous Headache Disorders.

Patient/contact via phone?	Diagnosis	Duration of implant (months)	Lead revision procedures	Overall benefit per patient or medical record	Would the patient repeat?	ONS deemed successful by investigator?	Notes
50 F/Yes	PT	48	0	50%	Yes	Yes	
46 F/Yes	HC	85	2	87%	Yes	Yes	
27 F/Yes	NPDH	71	0	70%	Yes	Yes	
48 M/Yes	PT	24	0	88%	Yes	Yes	Headaches resolved with move to higher elevation, explanted
74 M/Yes	ON	90	0	Pain resolved spontaneously	Not asked	Unable to determine	Stimulator not in use
56 M/Yes	PT	Unknown	0	Not effective	No	No	Explanted at outside institution; patient could not recall date
40 M/No	Unknown	14	1	"Excellent"	Unknown	Yes	Satisfied after lead revision, lost to follow-up
51 M/No	ON	9	1	"30% difference"	Unknown	No	
41 F/No	TAC, HC(?)	38	5	"Very poor control"	Unknown	No	
48 (13) years		379	9 revisions			5/8 (63%) success	

Success ≥ 50% benefit per patient or verbiage in the medical record suggesting significant improvement. Age presented as mean (standard deviation). Negative values denote reduction (in headache frequency, intensity, or MIDAS). Duration of implant, from time of implant to time of phone call or most recent clinical note.
F, female; M, male; MIDAS, migraine disability assessment score; NPDH, new persistent daily headache; HC, hemicrania continua; ON, occipital neuralgia; PT, posttraumatic; TAC, trigeminal autonomic cephalgia; ONS, occipital nerve stimulation.

Combining results from Tables 1 to 3, we find that of the 26 patients who underwent permanent ONS placement, ONS was deemed successful in five of the 12 migraine, four of the five cluster headache, and five of the eight miscellaneous headache patients, and therapy was documented as long as 102 months. As noted above (Table 3), success of ONS could not be determined in one of the 26 patients.

Table 4 summarizes frequency, severity, and MIDAS data for all patients. Not all data points for each endpoint were available for each patient due to our inability to contact the patient via phone, no recorded baseline, or no follow-up data in the medical record. Overall, frequency of headaches decreased by 12.8%, severity by 24%, and MIDAS by 49.9%. Table 5 provides similar data for the 14 patients in whom ONS was deemed successful by the investigators. Headache frequency decreased by 18%, severity by 27%, and migraine disability score by 49.9%. Of note in Table 4 (MIDAS), the six patients with both baseline and follow-up data that make up the percentage change are the same six patients in Table 5 for whom both baseline and follow-up data were available.

DISCUSSION

The results of this small, retrospective study of a heterogeneous patient population suggest that ONS may provide long-term benefit for patients with medically intractable primary headache disorders. In more than half of the patients, ONS was deemed successful by the investigators, and ten of the 14 patients contacted via phone stated that they would repeat the procedure.

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Table 4. Long-Term Headache Frequency, Severity, and MIDAS Changes for All Patients, *N* = 26.

	Baseline mean (SD)	Follow-up mean (SD)	% Change mean (SD)
Headache days (per 90 days)	87.8 (7.3)	76.1 (29.3)	−12.8 (38.3)
	N = 19	*N* = 16	*N* = 14
Severity (0–10)	7.2 (2.1)	5.7 (2.0)	−24.0 (31.5)
	N = 22	*N* = 17	*N* = 17
MIDAS	169.1 (96.8)	115.2 (124.4)	−49.9 (68.2)
	N = 7	*N* = 14	*N* = 6

MIDAS, migraine disability assessment score; SD, standard deviation.

Table 5. Long-Term Headache Frequency, Severity, and MIDAS Changes for All Patients With Successful Occipital Nerve Stimulation, *N* = 14.

	Baseline mean (SD)	Follow-up mean (SD)	% Change mean (SD)
Headache days (per 90 days)	86.8 (8.7)	68.7 (35.5)	−18.0 (44.9)
	N = 13	*N* = 10	*N* = 10
Severity (0–10)	7.5 (1.9)	5.3 (2.2)	−27.0 (38.3)
	N = 14	*N* = 11	*N* = 11
MIDAS	176.2 (104.1)	58.8 (60.8)	−49.9(68.2)
	N = 6	*N* = 10	*N* = 6

MIDAS, migraine disability assessment score; SD, standard deviation.

Among the headache subtypes, ONS was deemed successful in 42% of migraine and 80% of cluster headache patients. These long-term outcomes are noteworthy, considering that at our institution only severe and refractory patients are referred for ONS. As shown in Table 1, the migraine sufferers had failed numerous (6–19) preventative medications before ONS implantation. There are at present no guidelines for preventative medications for chronic migraine, although recent guidelines are available for episodic migraine (21). Onabotulinum toxin A is the only Food and Drug Administration approved treatment for chronic migraine.

In terms of technical problems, more than half of the patients required at least one lead revision surgery. More data and clinical experience are needed to guide lead anchoring techniques and internal pulse generator placement. The risk of lead migration remains high due to the highly mobile neck region and is a limitation of current hardware. Lead pathway length change may be less with an infraclavicular battery site compared with abdominal or buttock sites (22).

A number of recent studies have evaluated ONS in patients with chronic refractory cluster headache (5,11,23–27). Muller et al. treated seven chronic cluster headache patients with bilateral ONS for a follow-up period of 12 months (26). Treatment decreased headache intensity and the consumption of attack medication; six of the seven patients would fully recommend the operation. De Quintana-Schmidt et al. followed four cluster headache patients for six months who received bilateral ONS therapy (27). Frequency, intensity, and duration of headache were decreased; all four patients would recommend the procedure. Burns et al. described 14 chronic cluster headache patients treated with ONS for a follow-up of 17.5 months (range 4–35 months) with improvement in ten patients (5). Burns et al. also reported benefit in five of the six patients treated with ONS for chronic cluster headache in a follow-up of 13 months (range 6–21 months) (11). In our study, four or five cluster headache patients were judged to have had successful outcomes with ONS, up to 102 months of therapy.

Like cluster headache, there is little comparative literature available for long-term outcome of ONS in migraine patients. Saper et al. conducted a multicenter randomized, blinded, controlled study on the safety and efficacy of adjustable stimulation ONS in 28 chronic migraine patients for a three-month period (28). Thirty-nine percent of patients receiving adjustable stimulation experienced a significant reduction in intensity or frequency. This is similar to our 42% success in 12 migraine patients. In a heterogeneous group of headache sufferers, Trentman et al. measured outcomes in a one-year duration of eight patients who underwent ONS via a microstimulator; seven of the eight patients obtained reduction in disability (29).

The efficacy of ONS, possibly combined with stimulation of the supraorbital nerves (SONs), is of particular interest for patients with holocephalic symptoms. As summarized by Reed et al. (30), the existing literature on ONS suggests greater success of this modality in patients with occipital region symptoms vs. those with more diffuse cephalgias. Reed et al.'s study of seven chronic migraine patients implanted with both ONS and SON leads showed that a combination of ONS and SONs was superior to ONS alone (30). Further study is needed to clarify optimal stimulation targets (distal trigeminal, occipital, or both) and management for the various primary headache disorders (31–34).

Weaknesses of this study include its retrospective nature and small sample size. However, given the expenses involved and the off-label indication, large samples outside of a randomized controlled trial are unlikely to be forthcoming. Unfortunately, there were not enough patients in any category (migraine, cluster headache, etc.) to analyze diagnosis-specific outcome measures such as MIDAS, intensity, or headache frequency. In some cases, baseline or follow-up data were unavailable in the medical record.

Due to the interactive nature of the telephone survey, selection bias may have occurred (e.g., patients with better ONS outcomes may have been more willing to be interviewed). There is also potential bias in the assessment of ONS success by the investigators (based upon chart review) vs. an assessment based upon the

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patient's stated overall benefit (when contacted via phone). In addition, improvement could conceivably be explained by uncontrolled headache therapies or factors other than ONS that were implemented during the long follow-up period, though this is unlikely given the recalcitrant nature of this group of patients having failed aggressive outpatient, procedural, nonpharmacological, and inpatient therapies over the course of many years. Lastly, surgical methods and devices used for ONS implantation were not homogenous but varied during the 8.5-year study duration.

CONCLUSION

This small, retrospective study of refractory headache patients suggests that ONS can provide durable, effective therapy when more conservative therapies have failed. Technical problems including the need to revise leads impacted many patients, but despite this more than half of the patients were deemed treatment successes. Missing data preclude definitive conclusions regarding the efficacy of ONS; nonetheless, new therapeutic modalities are needed for disabling medically intractable primary headache disorders. Further randomized and controlled long-term studies of ONS are indicated.

Authorship Statements

A. Brewer, T. Trentman, and M. Ivancic collected and analyzed the data and prepared the manuscript. B. Vargas, A. Rebecca, R. Zimmerman, and D. Dodick contributed to study design and interpretation of data and reviewed the manuscript critically. D. Rosenfeld analyzed and interpreted the data and reviewed the manuscript critically. All authors approved the submitted version of the manuscript.

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COMMENTS

The data presented in this paper reflect single-institution experience with peripheral nerve stimulation (PNS) of the occipital nerves for a variety of headache conditions. The authors summarized results in their patients that were operated outside of multi-center prospective studies. Overall, as one may see, the authors trialed three to four patients per year (twenty-nine over an 8.5 year period), and the mix of diagnoses included migraines, cluster headaches, post-traumatic headaches, occipital neuralgias, and a few cases of persistent daily headaches, trigeminal autonomic cephalgias and hemicranias continua.

Although the scientific value of this series is rather minor as the series is small, inhomogeneous and retrospectively analyzed – and the value of phone questionnaire is rather low—the practical importance of this summary is quite high. Based on this, one can get a general idea of what may be expected from this approach in this group of patients. An implant-to-trial ratio of ~90%, long-term success of 40–80% depending on diagnosis, an almost 60% revision rate, and even ~10% of long-term curative improvement resulting either in not using device anymore or removing device altogether—these are the numbers that can be used as a reference for others, particularly since they are quite similar to what we and others reported based on other long-term institutional series.

As the experience grows, it may be possible to combine data from multiple individual centers into some kind of meta-analysis. Hopefully, such future analytic review would support the modality, define best and worst indications, and prompt device manufacturers to develop dedicated devices for PNS of the occipital nerves as it is hard to imagine that we continue using off-label hardware despite these high revision rates that would have been prohibitive in any other area of neuromodulation.

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Brewer, et al. from the Mayo Clinic in Scottsdale, Arizona have presented a non-industry supported retrospective review of patient records reflecting trialed and implanted occipital nerve stimulator systems in patients with intractable headache. Records were reviewed and phone interviews conducted where possible. The period of time spanned 8.5 years. Of the 29 patients whose records were reviewed during the 8.5 year study period, 12 could not be contacted, 3 had not gone on to permanent implantation, and 14 underwent both phone and record review. The reported results reflected at least the chart review and for those contacted, both the chart review and phone interviews. Five of 12 migraine patients, 4 of 5 cluster headache patients, and 5 of 8 miscellaneous headache patients were considered to have successfully been treated over a period as long as 102 months. The authors provide tables that are particularly useful, detailing important variables on each of the patients, identifying among the variables the number of preventive medications used, duration of implant, the need for lead revision, repeated procedures, the diagnosis, the value of Onabotulinum toxin A, and investigator determinations. Other variables assessed included disability scores, pain severity, and a breakdown of variables between those with and without successful implantation.

Clearly this study has significant design and practical flaws that compromise the power of its findings. Nonetheless, the detail provided and the long-term perspective reflected in this study offers readers information not easily found elsewhere in the neuromodulation literature. As the authors point out, it is very difficult to achieve more satisfactory data collection and a more acceptable research process for a retrospective analysis of an off-label and poorly funded interventional procedure. Unlike many neuromodulation studies, neither the patients' care nor the study was funded by industry. The authors have carefully delineated their process of collection and clinical conclusions and have done an admirable job of putting together what are likely to be meaningful observations. The tables were particularly useful, and the long-term observations give us perspective that is currently lacking in the literature. Because of the acknowledged weaknesses, the data cannot be leveraged as generalizable but at the very least serve to further the effort to define the utility of neuromodulation for intractable headache.

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It is more than a decade since Weiner and Reed (1) published what can only be described a landmark paper in this Journal in which they described a cohort of patients with intractable head pain focused in the occipital region who responded remarkably to a neuromodulatory approach to the problem. This issue of the Journal addresses a very practical clinical question that patients and payers need to know: how long do the effects last and are there side effects with time (2). The data beg the over-arching question of what will happen next in this very exciting field.

Neuromodulation using ONS has now been applied in to a number of primary headache disorders: migraine (3), cluster headache (4–6), hemicrania continua (7) and short-lasting neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)(8), and successfully to cervicogenic headache (9). These patients have generally been medically refractory by acceptable standards (10). It has been difficult to standardize the stimulation (11), and response rates have been about two-thirds for most indications. Longer term outcomes have been stable (12, 13), and problems predictable with lead migration and battery failure at the top of the problems. Mechanistically, ONS alters brain function by changing thalamic activation in migraine (14) or cortical activation in cluster headache (15), while in neither condition does it alter the underlying areas seen to be activated in the disorders (16). It is basic science is now being unraveled (17). The progress from laboratory to imaging to clinical trials offers an excellent example of bench to bedside translational research.

Brewer and colleagues (2) who have been consistently at the cutting edge of the field report on fourteen of twenty-nine patients followed in a study period that extends for 8½ years. Their results in migraine and cluster headache are line with the literature. They illustrate ONS is not a panacea, although for selected patients, in good hands, the long-term outcomes are simply excellent. Important among the outcomes they report a 50% reduction in disability. This rings true in practice and reflects that we may not have captured the benefit well in current trials. Most disappointing is the lead revision rate at 58%, which may suggest one important avenue moving forward is devices designed for cranial and high cervical use.

Perhaps the great issue in ONS has been the issues with clinical trials. The only fully reported placebo-controlled study ONSTIM at the time of writing showed a modest benefit (18). The PRISM study has been reported in abstract form; again placebo-controlled, the primary endpoint failed (19). A crucial element of the data to emerge was that patients with medication overuse did very much worse than those without that problem (19). The most recent St Jude study also failed the

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primary endpoint (20); it has not been possible to evaluate that outcome as the full publication is yet to come. None of these studies, as far as one can determine have been blinded in any usual sense of the word so that issue how to design new studies is moot. Other neuromodulatory approaches, such a transcranial magnetic stimulation- TMS (21), may offer some direction, although what would be a sham is very complex. ONS now has potential competitors, TMS, sphenopalatine ganglion stimulation (22), supraorbital nerve stimulation (23) and transcutaneous vagal nerve stimulation (24). Perhaps one thing is certain, deep brain stimulation (25), which has now failed one controlled trial (26), and can clearly result in death (27), should now be only considered when all has failed, and perhaps not even then given the rate of change of therapies.

Brewer and colleagues (2) have nicely set out where we are. ONS needs well designed controlled trials that address the blinding problem. It could do with better devices designed for the head. Given the current state of the art, ONS should only be used outside of controlled trials in experienced centers who can collect and disseminate their experience so we can learn. Patients with medication overuse should clearly not be implanted, and implants involving multiple sites should only be done in controlled circumstances. *Ad hoc* widespread use of ONS is inappropriate since it limits the pool of patients for studies and thus ultimately limits the good we can do for our patients by understanding and applying these exciting new techniques to all those disabled by headache disorders.

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