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External Trigeminal Nerve Stimulation for the Acute Treatment of Migraine: Open-Label Trial on Safety and Efficacy

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Objective: The aim of the current study is to assess the safety and efficacy of external trigeminal nerve stimulation (e-TNS) via a transcutaneous supraorbital stimulator as an acute treatment for migraine attacks.

Materials and Methods: This was a prospective, open-labeled clinical trial conducted at the Columbia University Headache Center (NY, USA). Thirty patients who were experiencing an acute migraine attack with or without aura were treated with a one-hour session of e-TNS (CEFALY Technology) at the clinic. Pain intensity was scored using a visual analogue scale (VAS) before the treatment, after the one-hour treatment session, and at two hours after treatment initiation. Rescue migraine medication intake was recorded at 2 and 24 hours.

Results: Thirty patients were included in the intention-to-treat analysis. Mean pain intensity was significantly reduced by 57.1% after the one-hour e-TNS treatment (-3.22 ± 2.40; $p < 0.001$) and by 52.8% at two hours (-2.98 ± 2.31; $p < 0.001$). No patients took rescue medication within the two-hour observation phase. Within the 24-hour follow-up, 34.6% of patients used a rescue medication. No adverse events or subjective complaints were reported.

Conclusions: The findings from this open-labeled study suggest that transcutaneous supraorbital neurostimulation may be a safe and effective acute treatment for migraine attacks, and merits further study with a double-blind, randomized, sham-controlled trial.

Keywords: Acute migraine treatment, clinical trial, neuromodulation

Conflict of Interest: Denise Chou received travel reimbursement from Cefaly Technology for presentation of this study at a conference. Denise Chou reports research grants from Teva, Capnia, and AstraZeneca, as well as consultation fees from Teva, Pernix, and Allergan, outside the submitted work. The remaining authors have no conflicts to disclose related to or outside the submitted work. None of the authors have received any personal fees from the sponsor, nor are any of the authors on the sponsor's medical board or under any consultant contract with the sponsor.

INTRODUCTION

Migraine is a common neurobiological disorder characterized by recurrent episodes of headache accompanied by sensory hypersensitivity, which can significantly impair quality of life (1–3). Acute treatments are used during a migraine attack with the objective to abort or reduce headache pain and restore normal function (4,5), while preventive treatments are intended to reduce attack frequency and severity (5–8).

Current acute migraine treatments are primarily pharmacologic approaches (7), with the most commonly used medications being analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and triptans (5,7–10). These drugs bear several contraindications and are associated with moderate to severe side-effects (9–11). In patients with frequent and/or prolonged migraine attacks, excessive consumption of acute migraine drugs may lead to headache chronification and medication overuse headache (10,12), which portends a worse outcome (5,7,13). Moreover, some patients (particularly those with chronic migraine) may become resistant to conventional migraine medications and thus do not achieve sufficient pain relief (13–18). Medication-related adverse effects and limited effectiveness highlight the need for non-pharmacologic therapies.

Recent studies suggest that neurostimulation may be a promising modality for the treatment of headache. Several neuromodulation techniques have been investigated in primary headache disorders. Percutaneous occipital nerve stimulation has shown mixed efficacy for chronic migraine prevention in three randomized, controlled studies but with high rates of adverse events (AEs), including

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infection and lead migration/implantation failure requiring surgical intervention (16,19,20). Combined occipital nerve and supraorbital nerve neurostimulation showed better efficacy than occipital nerve stimulation alone (21). However, patient functional status improved in the perioperative period but waned over the long-term follow-up (22). Sphenopalatine ganglion stimulation (SPG) has showed positive results mainly for the treatment of cluster headache (23). A small, open-labeled study with SPG stimulation in refractory migraine ($N = 11$ patients) yielded pain-freedom in two patients, pain reduction in three patients, and no response in five patients (one patient was not stimulated) (24). Non-invasive vagus nerve stimulation (nVNS) demonstrated clinical benefits beyond those with standard of care for cluster headache (25), but did not meet the primary efficacy endpoint in a sham-controlled trial for chronic migraine prevention (26). Nevertheless, results from an open-label, single-arm pilot study suggests that nVNS may be effective in the acute treatment of episodic migraine and has minimal adverse effects (27).

Transcutaneous supraorbital neurostimulation was initially found to produce a sedative effect in a double-blind, sham-controlled, cross-over study with healthy subjects (28). A subsequent multicenter, randomized, double-blind, sham-controlled trial revealed the efficacy, and safety of external trigeminal nerve stimulation (e-TNS) for the prevention of episodic migraine (29). The therapeutic efficacy in migraine prevention was recently corroborated in a larger open randomized trial (30). Safety and patient satisfaction have been further confirmed by a prospective study of 2313 patients (31). However, there is limited data regarding the use of e-TNS for the acute treatment of migraine, although many patients report pain relief with the use of e-TNS during migraine attacks. A pilot trial was conducted at the University of Liege (Belgium) on ten patients with episodic migraine who used e-TNS as an acute treatment during three migraine attacks. There was complete pain relief in 13% of attacks and delay of medication intake in 20% of attacks. The low efficacy rate was attributed to the short duration of the treatment session (20 min), which was deemed insufficient to provide sustained pain relief (32). Given this, we sought to investigate whether e-TNS applied for a longer duration (60 min) at a pulse frequency of 100 Hz (vs. 60 Hz used in the migraine prevention studies) could effectively and safely treat an acute migraine attack.

MATERIALS AND METHODS

This study was a monocentric, prospective, open-labeled clinical trial conducted at the Columbia University Headache Center (NY, USA). The study was approved by the ethics committee at Columbia University Medical Center (IRB-AAAO9752) and registered on ClinicalTrials.gov (identifier: NCT02411513). Written informed consent was obtained from all patients included in the study. All authors had full access to all study data.

Inclusion/Exclusion Criteria

Patients with migraine with or without aura were recruited at a standard care visit or from home if they were experiencing a migraine attack lasting for at least three hours, with pain intensity stabilized for at least one hour and no intake of acute migraine medications for the prior three hours. Inclusion criteria were the following: adult patients aged 18 to 65 years with a history of episodic or chronic migraine with or without aura, meeting the diagnostic criteria listed in ICHD-III beta (2013) section 1, migraine (1), with the exception of "complicated migraine" (i.e., hemiplegic migraine, migraine with brainstem aura, ophthalmoplegic migraine/recurrent painful ophthalmoplegic neuropathy, migrainous infarction), experiencing headache localized to the frontal, retro- or peri-orbital region(s), on one or both sides. Exclusion criteria were the following: 1) pregnancy; 2) treatment with onabotulinum toxin (e.g., Botox, Dysport, Xeomin) to the head in the prior four months; 3) supraorbital nerve blocks in the prior four months; 4) diagnosis of other primary or secondary headache disorders, except of medication overuse headache; 5) only temporal or occipital headache location; 6) use of opioids in the preceding three months; 7) use of abortive migraine medication within three hours prior to enrollment; 8) intolerance to supraorbital neurostimulation (allodynia); 9) implanted metal or electrical devices in the head; and 10) cardiac pacemaker or implanted or wearable defibrillator.

Study Design

Patients were asked to rate their pain severity (baseline score) using an eleven-point visual analogue scale (VAS) (from 0 = no pain to 10 = maximum pain). The e-TNS device was then applied and neurostimulation treatment was initiated with intensity increasing over the first 14 min. Patients who were able to tolerate the paresthesia sensation for the first five minutes (reaching a minimum intensity of 7 mA or a minimum electrical dose of 1.75 μC per impulse) without having to level off the intensity were included and subsequently continued neurostimulation for the 55 remaining minutes. Those patients who were unable to tolerate the initial test phase were not enrolled, on the basis of the allodynia exclusion criterion (low nociceptive forehead skin threshold). At the completion of the one-hour treatment phase, patients were asked to rate their pain intensity (one-hour score) and again one hour post-treatment (two-hour score). Use of rescue medications was recorded at the two-hour mark; patients were also contacted the following day regarding use of rescue medications within 24 hours following the e-TNS treatment. Patients who took rescue medication before the end of the post-treatment phase were deemed a drop-out. The study design is illustrated in Figure 1.

Neurostimulation

e-TNS was applied via the Cefaly® neurostimulator device (CEFALY Technology, Seraing, Belgium) for a 60-min treatment session. The device is a constant current generator for a maximum skin impedance of 2.2 kΩ that delivers rectangular biphasic symmetrical pulses with a zero electrical mean. In the current study, the device was programmed with a pulse frequency of 100 Hz (vs. 60 Hz in the migraine prevention studies) and a pulse width of 250 μsec; the total maximum dose of current delivered by a one-hour treatment session is 1.284 Coulomb. The electrical impulses are transmitted transcutaneously via a supraorbital bipolar electrode (30 mm $\times$ 94 mm) designed to cover and excite (trigger action potentials) on both sides of the supratrochlearis and supraorbitalis nerves (Fig. 2). The intensity increases linearly to reach a maximum of 16 mA after 14 min and then stays constant for 46 min. If the patient feels that the stimulation is too strong, a single press on the device's button will stabilize the intensity for the remainder of the session (in this event, the patient receives a lower total current dosage).

Outcome Measures

Patients scored their pain intensity on a VAS with eleven levels (from 0 = no pain to 10 = maximum pain). Pain level was assessed before the treatment was applied (baseline score), after the one-hour treatment (one-hour score), and at two hours after the beginning of the treatment phase (two-hour score). Rescue medication

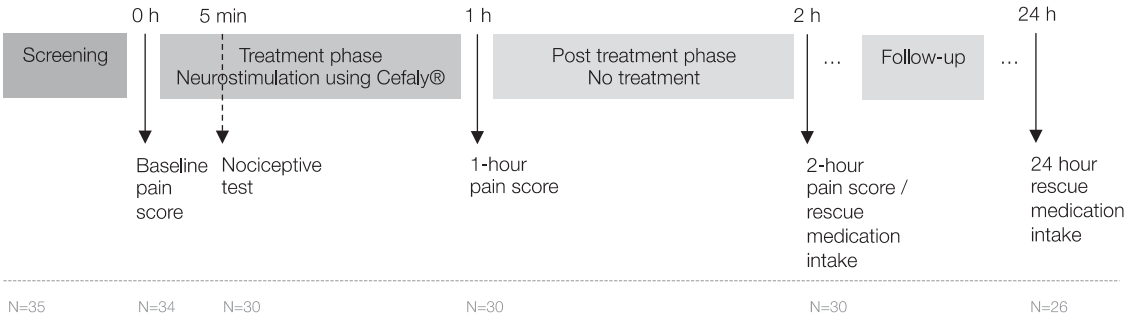

Figure 1. Study design.

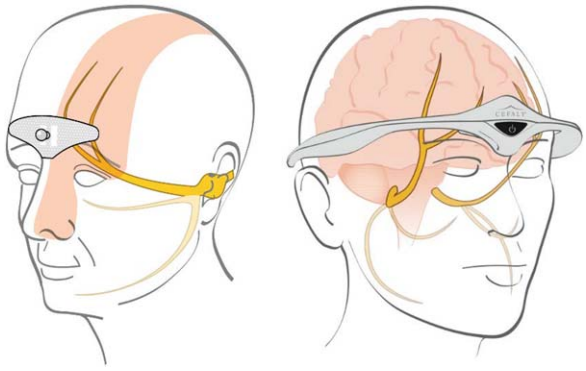

Figure 2. Cefaly electrode covering the supratrochlearis and supraorbitalis nerves, and the Cefaly device placed on the forehead. [Color figure can be viewed at wileyonlinelibrary.com]

intake was also recorded at two and 24 hours. Primary outcome was the mean change in pain intensity after the one-hour treatment, compared to baseline. Secondary outcomes were mean change in pain intensity at two hours after the start of treatment compared to baseline, as well as the percentage of patients not requiring rescue medication at two and 24 hours following the treatment.

Statistical Analysis

Analysis was conducted on a modified intention-to-treat (mITT) basis of the eligible subjects (i.e., those who were administered the treatment and for whom there was a baseline severity measurement). For each subject, the outcome was calculated using all available data during each period, without any imputation of missing data. Comparison between baseline and treatment results was performed using the Wilcoxon Signed Rank test for paired samples.

RESULTS

The trial was conducted from April 2015 through October 2015. In total, 35 patients were screened. One patient was excluded due to use of opioid medication within the prior three months and four patients failed the nociceptive test (two patients were not able to tolerate early stimulation during the test phase and another two were excluded due to unintentional disconnection of the device from the electrode by the patient during the test phase). The remaining 30 patients received the full one-hour stimulation, with zero drop-out during the study (Fig. 1). Patient demographic characteristics are shown in Table 1. No AEs occurred, nor were any subjective complaints reported during or within 24 hours after the treatment.

Table 2 presents the study outcomes. There was a statistically significant decrease in pain intensity, both after the one-hour treatment

Table 1. Patient Demographics.

Number of patients included	30
Age (years)	39.4 ± 12.5
Number of female	24 (80.0%)

Data are expressed as *n*, mean ± SD or *n* (%).

Table 2. Study Results.

Primary outcome	
Change in pain intensity after one hour of treatment, compared to baseline	−3.22 ± 2.40 ($p < 0.001$*)
Secondary outcomes	
Change in pain intensity two hours after treatment initiation, compared to baseline	−2.98 ± 2.31 ($p < 0.001$*)
Percentage of patients not having required rescue medication at two hours	100.0%
Percentage of patients not having required rescue medication within 24 hours†	65.4%
Supplementary results	
Patients reporting ≥30% pain relief at one hour	25 (83.3%)
Patients reporting ≥30% pain relief at two hours	21 (70.0%)
Patients reporting ≥50% pain relief at one hour	23 (76.7%)
Patients reporting ≥50% pain relief at two hours	17 (56.7%)
Patients reporting pain freedom at one hour	6 (20.0%)
Patients reporting pain freedom at two hours	4 (13.3%)

Data are expressed as mean ± SD, % or *n* (%).
*p-Values were calculated using the Wilcoxon Signed Rank test for paired samples.
†Missing data for four patients.

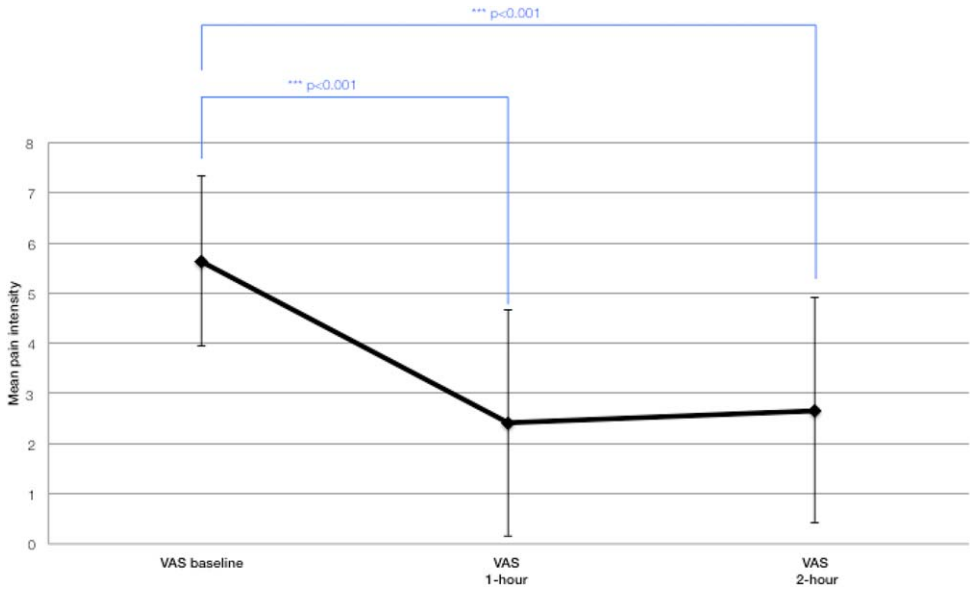

Figure 3. Change in mean pain intensity (VAS score) ranging from 0 to 10. (Data are presented as mean ± SD.). [Color figure can be viewed at wileyonlinelibrary.com]

and at two hours after treatment initiation. No patients used rescue medication at the end of the two-hour period. Patients were also contacted 24 hours after the treatment to report whether they used rescue medication during that time frame. Of the 26 patients who were successfully contacted, 17 patients (65.4%) did not use rescue medication within the 24 hours following the treatment.

Figure 3 presents the change in mean pain intensity. On average, pain intensity was reduced from 5.63 to 2.42 after one hour of treatment and to 2.66 at two hours. This reduction was statistically significant in both cases ($p < 0.001$).

It is also interesting to note the proportion of patients reporting pain relief (and the degree thereof), as well as pain freedom. As shown in Table 2, 76.7% of patients reported $\geq$50% pain relief at one hour and 56.7% at two hours. Six patients (20.0%) reported pain freedom at one hour, and four patients (13.3%) at two hours.

Regarding the neurostimulation intensity, 17 patients (56.7%) tolerated the maximum intensity of 16 mA (i.e., received the full dose of current of 1.284 Coulomb) and 13 patients (43.3%) required the stimulation intensity to be limited at an average of 9.51 mA. Subanalysis comparing the group of 13 patients who limited the current output and the group of 17 patients who received the total electrical dose revealed a difference only in use of rescue medication intake within 24 hours: 50% of patients receiving partial current output used rescue medication, compared to 25% of patients who received the full current dose. However, data were only available for 10 and 16 patients in each group, respectively, and the difference was not statistically significant ($p = 0.234$). Baseline pain scores were similar between the two groups ($p = 0.240$): mean score of 6.0 for the 13 patients who limited current output during the stimulation vs. mean score of 5.4 for the 17 patients who received the total electrical dose.

DISCUSSION

The objective of this open-label pilot trial was to assess the safety and efficacy of e-TNS as an acute treatment for migraine attacks in adult patients.

Concerning safety, no AEs or complaints were reported during the trial, which confirms the minimal risk level of the treatment. This was also demonstrated in a retrospective study on the prevention of episodic migraine in 2313 patients, of whom only 4.3% reported adverse effects (31) (including 2.0% with intolerance to paresthesia). In our study, two out of 34 patients (5.9%) were not enrolled due to failure of the tolerance test. This higher percentage of intolerance to paresthesia could be explained by increased allodynia during migraine attacks (33–35). Interestingly, there was no increase in skin irritation with the longer 60-min session, compared to the 20-min session used in prior studies.

With regards to efficacy, mean pain intensity was significantly reduced by 57.0% after the one-hour treatment and by 52.8% at two hours. The similar rate at the two time points indicates that pain reduction is well-maintained for at least an hour after the end of the neurostimulation. The percentage of patients not using rescue medication was 100% after two hours and 65.4% after 24 hours. The proportion of patients not taking rescue medication within 24 hours in placebo groups for pharmacologic acute migraine treatment trials is usually reported to be around 32% (36); however, the subject population and treatment protocol in our study differ from acute medication trials which render the comparison difficult. Therefore, while the efficacy data here are promising, it should be taken into account that the study was open-labeled and treatment in the clinic setting may accentuate the placebo effect. Conversely, treatment in the clinic ensures appropriate application/use of the device and proper collection of data. Of further consideration is that patients were recruited at a minimum of three hours into a migraine attack to ensure a stable baseline pain intensity; however, it is known that acute pharmacologic treatments are more effective when used earlier in a migraine attack. The effectiveness of e-TNS even when used late in a migraine attack is thus encouraging.

Comparison with published data for other acute migraine treatments is limited because of differences in trial design. Nevertheless, one study reported a reduction in mean pain VAS scores at one hour of 26.8% for diclofenac and 17.1% for sumatriptan (37), compared to 57.1% for e-TNS in our study. At two hours, mean pain score reductions were 50.5% for diclofenac, 40.0% for sumatriptan, and 52.7% with e-TNS.

Regarding rescue medication intake, a recent review on triptans for the acute treatment of migraine (38) reported that use of rescue medication after a standard dose triptan ranged from 20 to 34% and averaged 37% for NSAIDs, vs. 34.6% for e-TNS between 2 and 24 hours. Notwithstanding the limitation of these comparisons due to differences in study design, the data suggest a similarity in efficacy with respect to rescue medication use. Again, it should be noted that the e-TNS treatment was applied later in a migraine attack (at least three hours) than the above acute migraine medications, which have shown better efficacy when administered early into an attack.

No dose response data for e-TNS are available in the literature and to the best of our knowledge, we report here the first comparison between a group who received full e-TNS stimulation intensity (16 mA) and a group with limited current output (average of 9.51 mA). Although the results are slightly better for the group receiving the full intensity, only rescue medication intake within 24 hours was noticeably different but not statistically significant. Larger sample sizes would be needed to determine whether a higher dose of current yields better and more sustained pain relief, therefore resulting in lower rescue medication intake within 24 hours after the treatment. It should be noted that the initial pain scores were similar between the patients who limited the current output and those who received the total current dose, suggesting that intolerance to neurostimulation is not merely a function of baseline pain severity and that patients who failed the nociceptive threshold test (and thus excluded from the study) did not simply have more severe pain to begin with.

With respect to the duration of treatment, a previous pilot study showed that only 33% of patients experienced pain relief with a 20-min session of e-TNS to treat a migraine attack (32). In the current study, we used a one-hour treatment session, which yielded higher rates of pain relief (76.7% of patients had $\geq$50% pain relief after stimulation [Table 2]).

CONCLUSION

The results of this open pilot trial on the use of e-TNS as an acute treatment for migraine are encouraging with regards to both safety and efficacy, and warrant further confirmation with a phase II, multicenter, double-blind, randomized, sham-controlled study.

Authorship Statements

Denise Chou designed and conducted the study (including patient recruitment, data collection, statistical analysis, and interpretation of data), drafted the manuscript, and provided overall supervision for the study. Giti Gross and Camilla Casadei assisted with patient recruitment/enrollment, acquisition of data, and revision of the manuscript. Marianna Yugrakh assisted with patient recruitment, contributed to the analysis and interpretation of the data, as well as revising the manuscript for intellectual content.

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REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629–808.
2. Abu Bakar N, Tanprawate S, Lambru G, Torkamani M, Jahanshahi M, Matharu M. Quality of life in primary headache disorders: a review. *Cephalalgia* 2016;36:67–91.
3. Lantéri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. *Cephalalgia* 2011;31:837–850.
4. Dougherty C, Silberstein SD. Providing care for patients with chronic migraine: diagnosis, treatment, and management. *Pain Pract* 2015;15:688–692.
5. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache* 2015;55:103–122.
6. Silberstein SD. Preventive migraine treatment. *Neurol Clin* 2009;27:429–443.
7. Steiner TJ, Paemeleire K, Jensen R et al. European principles of management of common headache disorders in primary care. *J Headache Pain* 2007;8:S3–47.
8. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American headache society evidence assessment of migraine pharmacotherapies. *Headache* 2015;55:3–20.
9. Evers S, Afra J, Frese A et al. EFNS guideline on the drug treatment of migraine – revised report of an EFNS task force. *Eur J Neurol* 2009;16:968–981.
10. Lanteri-Minet M, Valade D, Geraud G, Lucas C, Donnet A. Revised French guidelines for the diagnosis and management of migraine in adults and children. *J Headache Pain* 2014;15:2.
11. Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. *Headache* 2003;43:36–43.
12. Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2013;53:1300–1311.
13. Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. *Lancet Neurol* 2012;11:708–719.
14. Cruccu G, Aziz TZ, Garcia-Larrea L et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007;14:952–970.
15. Lambru G, Matharu MS. Peripheral neurostimulation in primary headaches. *Neurol Sci* 2014;35:77–81.
16. Saper JR, Dodick DW, Silberstein SD et al. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. *Cephalalgia* 2011;31:271–285.
17. Schwedt TJ. Occipital nerve stimulation for medically intractable headache. *Curr Pain Headache Rep* 2008;12:62–66.
18. Schwedt TJ. Neurostimulation for primary headache disorders. *Curr Neurol Neurosci Rep* 2009;9:101–107.
19. Silberstein SD, Dodick DW, Saper J et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. *Cephalalgia* 2012;32:1165–1179.
20. Lipton RB, Goadsby PJ, Cady RK et al. PRISM study: occipital nerve stimulation for treatment-refractory migraine (abstract). *Cephalalgia* 2009;29:30.
21. Reed KL, Black SB, Banta CJ, Will KR. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. *Cephalalgia* 2010;30:260–271.
22. Clark SW, Wu C, Boorman DW et al. Long-term pain reduction does not imply improved functional outcome in patients treated with combined supraorbital and occipital nerve stimulation for chronic migraine. *Neuromodulation* 2016;19:507–514.
23. Schoenen J, Jensen RH, Lantéri-Minet M. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. *Cephalalgia* 2013;33:816–830.
24. Tepper SJ, Rezai A, Narouze S, Steiner C, Mohajer P, Ansarinia M. Acute treatment of intractable migraine with sphenopalatine ganglion electrical stimulation. *Headache* 2009;49:9.
25. Gaul C, Diener HC, Silver N et al. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): a randomized controlled study. *Cephalalgia* 2016;36:534–546.
26. Silberstein SD, Calhoun AH, Lipton RB. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: the EVENT study. *Neurology* 2016;87:529–538.
27. Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. *Cephalalgia* 2014;34:986–993.
28. Piquet M, Balestra C, Sava SL, Schoenen JE. Supraorbital transcutaneous neurostimulation has sedative effects in healthy subjects. *BMC Neurol* 2011;11:135.
29. Schoenen J, Vandersmissen B, Jeangette S et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology* 2013;80:697–704.
30. Russo A, Tessitore A, Conte F, Marcuccio L, Giordano A, Tedeschi G. Transcutaneous supraorbital neurostimulation in "de novo" patients with migraine without aura: the first Italian experience. *J Headache Pain* 2015;16:69.
31. Magis D, Sava S, d'Elia TS, Baschi R, Schoenen J. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population. *J Headache Pain* 2013;14:95.
32. Gérardy P, Fabry D, Fumal A, Schoenen J. A pilot study on supra-orbital surface electrotherapy in migraine. *Cephalalgia* 2009;29:134.

33. Ashkenazi A, Silberstein S, Jakubowski M, Burstein R. Improved identification of allodynic migraine patients using a questionnaire. *Cephalalgia* 2007;27: 325–329.
34. de Tommaso M, Guido M, Libro G et al. Abnormal brain processing of cutaneous pain in migraine patients during an attack. *Neurosci Lett* 2002;333:29–32.
35. Lipton RB, Bigal ME, Ashina S et al. Cutaneous allodynia in the migraine population. *Ann Neurol* 2008;63:148–158.
36. Färkkilä M, Diener HC, Géraud G et al. Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol* 2012; 11:405–413.
37. The Diclofenac-K/Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison to oral sumatriptan and placebo. *Cephalalgia* 1999;19: 232–240.
38. Cameron C, Kelly S, Hsieh S-CC et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache* 2015;55: 221–235.

