Chronic migraine headache prevention with noninvasive vagus nerve stimulation

The EVENT study

Objective: To evaluate the feasibility, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS) for the prevention of chronic migraine (CM) attacks.

Methods: In this first prospective, multicenter, double-blind, sham-controlled pilot study of nVNS in CM prophylaxis, adults with CM (≥15 headache d/mo) entered the baseline phase (1 month) and were subsequently randomized to nVNS or sham treatment (2 months) before receiving open-label nVNS treatment (6 months). The primary endpoints were safety and tolerability. Efficacy endpoints in the intent-to-treat population included change in the number of headache days per 28 days and acute medication use.

Results: Fifty-nine participants (mean age, 39.2 years; mean headache frequency, 21.5 d/mo) were enrolled. During the randomized phase, tolerability was similar for nVNS (n = 30) and sham treatment (n = 29). Most adverse events were mild/moderate and transient. Mean changes in the number of headache days were −1.4 (nVNS) and −0.2 (sham) (Δ = 1.2; p = 0.56). Twenty-seven participants completed the open-label phase. For the 16 participants initially assigned to nVNS, the mean change from baseline in headache days was −3.6 (95% confidence interval −6.3 to −0.87; p = 0.02).

Conclusions: Therapy with nVNS was well-tolerated with no safety issues. Persistent prophylactic use may reduce the number of headache days in CM; larger sham-controlled studies are needed.

ClinicalTrials.gov identifier: NCT01667250.

Classification of evidence: This study provides Class II evidence that for patients with CM, nVNS is safe, is well-tolerated, and did not significantly change the number of headache days. This pilot study lacked the precision to exclude important safety issues or benefits of nVNS. Neurology® 2016;87:1–10

GLOSSARY

AE = adverse event; CI = confidence interval; CM = chronic migraine; ITT = intent-to-treat; LOCF = last observation carried forward; nVNS = noninvasive vagus nerve stimulation; PP = per-protocol; SAE = serious adverse event; VNS = vagus nerve stimulation.

Migraine is a disabling neurologic headache disorder with symptoms including nausea and sensitivity to light/sound. Compared with episodic migraine (headache occurring <15 d/mo), chronic migraine (CM; headache occurring ≥15 d/mo) leads to greater disability and lower productivity. Although preventive β-blockers, tricyclic antidepressants, and anticonvulsants are used off-label in CM, onabotulinumtoxinA is the only approved prophylactic CM medication.5

Supplemental data at Neurology.org

From Jefferson Headache Center (S.D.S.), Philadelphia, PA; Carolina Headache Institute (A.H.C.), Chapel Hill, NC; Montefiore Headache Center and Albert Einstein College of Medicine (R.B.L.), Bronx, NY; Hartford HealthCare Headache Center (R.M.G.), West Hartford, CT; Clínica Headache Care Center (R.K.C.), Springfield, MO; MedLogix Communications, LLC (S.D.), Schaumburg, IL; electroCore, LLC (K.A.S., J.R.S.), Basking Ridge, NJ; NAMSA (C.M.), Minneapolis, MN; University of California San Francisco (P.J.G.); King’s College London (P.J.G.), UK; and Michigan Headache and Neurological Institute (J.R.S.), Ann Arbor. B.M.G. was affiliated with Montefiore Headache Center, Bronx, NY, at the time of study completion.

Coinvestigators are listed on the Neurology® Web site at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article. The Article Processing Charge was paid by electroCore, LLC.

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The remaining 4 sites. All participants provided signed informed consent. The study was approved by the Research Alliance of New York institutional review board for safety and tolerability of nVNS; it was to assess the feasibility, safety, and tolerability of nVNS; however, this association has not been investigated in migraine prophylaxis.

Despite the potential benefits of implanted VNS therapy, the high risks and costs of surgical implantation have hindered its clinical evaluation. A patient-controlled, handheld, noninvasive VNS (nVNS) device (gammaCore®; electroCore, LLC, Basking Ridge, NJ) has been CE-marked for the treatment of primary headache disorders (including migraine). Here we describe preliminary experience with nVNS for CM prophylaxis. These data were first reported at the 56th annual meeting of the American Headache Society (June 26–29, 2014; Los Angeles, CA).

METHODS Primary objective. The objective of this study was to assess the feasibility, safety, and tolerability of nVNS; it was not powered to assess efficacy.

Standard protocol approvals and patient consents. The protocol was approved by site-specific institutional review boards for 2 of the 6 participating sites and by the Biomedical Research Alliance of New York institutional review board for the remaining 4 sites. All participants provided signed informed consent before enrollment.

Study design. This prospective pilot study of nVNS for CM prophylaxis was conducted at 6 US tertiary care headache centers between October 2012 and April 2014 (EVENT; ClinicalTrials.gov NCT01667250). The study comprised 3 consecutive phases: a third-party distributor provided the devices to study sites. An unblinded trainer provided participants with the devices and instructions on device features, proper use, and treatment schedules. Participants, investigators, and study coordinators were blinded to treatment assignment during the randomized phase.

Interventions. The nVNS device produced a proprietary electrical signal that delivered a low voltage (peak, 24 V) and a maximum output current of 60 mA. Users adjusted the stimulation amplitude within a preset range. Two stainless steel contact surfaces coated with a conductive gel enabled delivery of stimulations to the neck in the vicinity of the vagus nerve (figure e-1 on the Neurology® Web site at Neurology.org). The sham device was identical in appearance, weight, visual and audible feedback, and user application and control but did not deliver electrical stimulations. Each treatment consisted of two 2-minute self-administered stimulations delivered 5–10 minutes apart to the right side of the neck at 3 prespecified times every day: (1) within 1 hour of awakening; (2) 6–8 hours after the first treatment; and (3) 6–8 hours after the second treatment. Acute headache medication use was permitted throughout the study.

Assessments and endpoints. Participants used diaries to record safety and tolerability (primary endpoints), efficacy, and satisfaction data. Investigators categorized the onset, type, severity (mild, moderate, severe), and frequency of adverse events (AEs) according to treatment relatedness. Serious AEs (SAEs) were defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Good Clinical Practice.

The number of reported headache days per month was normalized to the number of headache days per 28 days, which was the primary efficacy measure. A headache day was defined as any day on which a participant recorded a headache. The mean change from baseline in the number of headache days was evaluated at the end of the randomized phase (month 2) and through the end of the open-label phase (at 4, 6, and 8 months of treatment). Post hoc efficacy analyses assessed the effect of treatment duration on the number of headache days and determined the percent treatment response, defined as the proportion of participants who demonstrated ≥50% reduction from baseline in the number of headache days.

The rate of patient-reported acute medication use and treatment adherence, satisfaction, and ease of use were evaluated throughout both phases. Treatment adherence ([actual number of administered treatments]/([total number of scheduled treatments] × 100) was calculated as the average daily adherence. Treatment satisfaction was assessed on a 5-point scale (extremely satisfied to not at all satisfied). Ease of use was rated on a 4-point scale (very easy...
RESULTS  Participants. Fifty-nine of the 73 participants in the baseline phase were eligible for randomization and constituted the ITT population (nVNS, n = 30; sham, n = 29) (figure 1). A total of 51 participants (nVNS, n = 26; sham, n = 25) from the ITT population and 49 participants (nVNS, n = 26; sham, n = 23) from the PP population (i.e., no violations) completed the randomized phase, and 48 participants (nVNS, n = 24; sham, n = 24) from the ITT population and 47 participants (nVNS, n = 24; sham, n = 23) from the PP population continued into the open-label phase. Twenty-seven participants completed the study (nVNS, n = 16; sham, n = 11). Safety analyses were performed on all 59 participants from the ITT population. Demographic and baseline characteristics were similar to those reported in other migraine studies (table 1). Participants (mean age, 39 years; mean headache frequency, >20 d/mo) were predominantly Caucasian women.

Safety and tolerability. The tolerability profile of nVNS was satisfactory and generally similar to that of sham treatment (table 2). Most AEs were mild or moderate and transient. The most commonly reported AEs were upper respiratory tract infections and gastrointestinal symptoms. During the randomized phase, 6 nVNS-treated participants reported 12 AEs that were related or possibly related to the device, whereas 5 controls reported 8 such AEs. No SAEs occurred during the randomized phase. During the open-label phase, 5 participants reported 8 AEs that were related or possibly related to the device. Two participants reported SAEs during the open-label phase (i.e., appendicitis and worsening headache); both were unrelated to the device. No discontinuations due to device-related AEs occurred.

Number of headache days. The mean number of headache days in the nVNS group (n = 30) was 20.8 (95% CI 18.9–22.6) at baseline and 19.4 (95% CI 16.6–22.1) at month 2 (end of the randomized phase), representing a mean change of −1.4 (95% CI −3.7 to 0.77; p = 0.44) (figure 2A). The mean number of headache days in controls (n = 29) was 22.3 (95% CI 20.4–24.1) at baseline and 22.0 (95% CI 19.5–24.6) at month 2, demonstrating a mean change of −0.2 (95% CI −1.5 to 1.1; p = 0.72) (figure 2A). The mean change from baseline was not statistically different between groups (p = 0.56). The difference between groups was slightly more pronounced in the PP population, with mean changes of −2.0 (95% CI −4.4 to 0.4) for nVNS and −0.1 (95% CI −1.6 to 1.4) for sham (p = 0.35). Persistent prophylactic nVNS use was associated with continued reductions in the number of headache days. After the open-label phase, participants initially assigned to nVNS had a mean of 17.2 (95% CI 13.8–20.5) headache days and a mean change from baseline of −3.6 (95% CI −6.3 to −0.87; p = 0.02) after 8 months of treatment (figure 2A). Participants initially randomized to sham treatment had a mean of 19.7 (95% CI 16.5–23.0) headache days and a mean change from baseline of −2.5 (95% CI −5.0 to −0.04; p = 0.06) after 6 months of nVNS (figure 2A). To investigate the effect of treatment persistence, mean changes in the number of headache days were analyzed without LOCF imputation. More pronounced and clinically meaningful reductions from baseline at months 4, 6, and 8 (−3.7, −6.1, and −8.0 headache days, respectively) were observed in the nVNS group (month 4, p < 0.05; months 6 and 8, p < 0.01). The mean change of −6.0 headache days for controls reached statistical significance at month 8 (p < 0.05).

In the PP completer population, longer duration was associated with greater reductions in headache days from study baseline (nVNS) and from month 2 (sham) (figure 2B). These mean reductions were 1.6 (95% CI 0.1–3.1; p = 0.06) for 2-month completers (n = 44), 3.9 (95% CI 1.4–6.3; p = 0.004) for 4-month completers (n = 32), 6.2 (95% CI 3.2–9.3; p < 0.0001) for 6-month completers (n = 26), and 7.9 (95% CI 11.9–3.8; p = 0.0009) for 8-month completers (n = 15) (figure 2B). In contrast with 2-month
completers, 4-, 6-, and 8-month completers each experienced significant reductions at 2-, 4-, 6-, and 8-month timepoints except for the 8-month completers at the 2-month timepoint ($p = 0.06$) (figure 2B).

**Treatment response.** At month 2, 10.0% (3/30) of participants from the nVNS group had a $50\%$ response, and 3.3% (1/30) experienced a $75\%$ response. No controls experienced a $50\%$ response. In the PP population, 11.5% (3/26) of participants from the nVNS group had a $50\%$ response; 3.8% (1/26) experienced a $75\%$ response. No controls experienced a $50\%$ response. In the PP completer populations, the proportion of participants who achieved a $50\%$ response increased with longer duration of treatment throughout the open-label phase (figure 3).

**Acute medication use.** Rates of acute medication use were comparable between groups and remained stable from baseline (89.8%) through the open-label phase (81.5%).

### Table 1 Participant demographics and baseline characteristics

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Abbreviations: BMI = body mass index; nVNS = noninvasive vagus nerve stimulation.

*Percentage totals in some columns are either <100% or >100% because of rounding.
Treatment adherence, satisfaction, and ease of use. Mean treatment adherence for both groups was $\geq 95\%$ during the randomized phase and $\geq 92\%$ during the open-label phase. At month 2, 58.3% (14/24) of nVNS-treated participants and 41.7% (10/24) of sham-treated participants were at least a little satisfied with treatment ($p = 0.25$; $\chi^2$ test). Among participants who completed the open-label phase, 88.5% (23/26) were satisfied with treatment. Most participants found the device somewhat easy or very easy to use (nVNS, 20/24; 83.3%; sham, 22/24; 91.7%).

Blinding evaluation. At the beginning of the randomized phase, a similar number of participants in each arm (nVNS, 37.9% [11/29]; sham, 39.3% [11/28]) correctly identified their treatment. The groups had similar Bang index values (nVNS, 0.31 [95% CI 0.15–0.47]; sham, 0.32 [95% CI 0.15–0.49]), each indicating that blinding was not achieved. At month 2, Bang index values of 0.04 (95% CI 0.0.0–0.25) for nVNS and 0.54 (95% CI 0.31–0.77) for sham suggest blinding was achieved in the nVNS group but not in controls.

DISCUSSION We demonstrated that nVNS for CM prevention was well-tolerated and identified no safety issues; preliminary efficacy results showed that the reduction in headache days during the 2-month randomized phase among participants receiving nVNS compared with controls was not significant. We assessed whether longer treatment duration was associated with clinically meaningful results, as previously reported in a study of neuromodulation in CM. Participants originally randomized to nVNS and who continued open-label treatment for 6 months had a significant reduction from baseline in the number of headache days. Longer treatment durations were associated with greater reductions in number of headache days and higher $\geq 50\%$ response rates, recognizing that the 27 participants who completed the open-label phase of the trial and...
received longer treatment (16 and 11 of whom were initially randomized to nVNS and sham, respectively) may have been self-selected.

Among study completers, the ≥50% response rate increased with time on treatment, which supports the slow accrual of clinical benefits over time reported in VNS studies of epilepsy and depression.6,7 Loss to follow-up cannot explain this result; however, regression toward the mean may be a confounding factor. The association between longer nVNS treatment duration
and a gradual reduction in headache days suggests that participants who discontinued the study might have benefited from continued treatment, consistent with other findings in the literature.6,7,19 Conversely, participants who continued treatment may represent self-identified responders for whom the device is effective.

Study limitations included the small sample size, blinding challenges, and high discontinuation rate. Blinding in device studies is challenging, especially in comparison with drug studies.20 Our sham device was identical to the nVNS device but did not deliver an active signal. A sham device should mimic the functionality and sensation of active treatment without producing treatment effects or device-related AEs. Missing data and high discontinuation rates occurring disproportionately across treatment groups can affect study outcomes. In this study, discontinuation rates were higher in controls than in the nVNS group; however, no discontinuations stemmed from device-related AEs.

The emergence of noninvasive neuromodulation devices has sparked interest in their application in migraine therapy. Two short-term, double-blind, randomized, controlled trials have examined prophylactic therapy for migraine using noninvasive neuromodulation devices.21,22 One multicenter sham-controlled study reported a significant reduction in the mean number of headache days following transcutaneous supraorbital stimulation for 3 months in participants with migraine; however, the proportion of participants with CM was unknown.21 A single-center controlled study of prophylactic transcutaneous auricular VNS therapy in CM showed that the reduction in number of headache days was significantly greater at a stimulation frequency of 1 Hz than at 25 Hz; however, no sham arm was available for comparison.22 EVENT is the first multicenter, double-blind, randomized, sham-controlled trial to demonstrate the long-term (8-month) tolerability and preliminarily evaluate the efficacy of prophylactic nVNS therapy in a clinically defined CM population. Stimulation parameters used in EVENT (i.e., 2-minute stimulations administered 3 times per day on the right side of the neck) were based on both previous open-label clinical studies in migraine and cluster headache and preclinical models of migraine and airways disease,25–27 but bilateral stimulations are currently being used in ongoing studies, which may affect efficacy results observed in these and future trials. Findings from the animal migraine models suggest that nVNS may exert beneficial effects via the suppression of glutamate levels and cortical spreading depression, a key factor in migraine pathophysiology.25,27 Prophylactic nVNS has been shown to be clinically beneficial19 and cost-effective28 in chronic cluster headache. Findings from EVENT expand the evidence regarding the potential role of noninvasive neuromodulation in headache therapy. Given the need for novel prophylactic therapies for CM and the high cost of the currently approved medication,29,30 nVNS

Figure 3 Participants who achieved a ≥50% treatment response with noninvasive vagus nerve stimulation (nVNS) (per-protocol completer population)

![Graph showing treatment response](image)

*The 2-, 4-, and 6-month completers were from the 59 participants initially randomized to either nVNS or sham treatment.
*The 8-month completers were from the 30 participants initially randomized to nVNS treatment. *One participant who completed 8 months of nVNS initiated gabapentin treatment during the study and was therefore excluded from 8-month completer analyses.
may serve as a well-tolerated and potentially cost-effective alternative for patients with CM.

nVNS is a highly feasible, well-tolerated, and convenient therapy. Although self-selection bias is associated with the long-term findings, the continued reduction in headache days over the 6-month open-label phase suggests that nVNS may offer a clinical benefit to patients with CM. Longer-term use of nVNS in treatment responders would be reflective of clinical practice.31 On the basis of the lack of a plateau in effects seen during the open-label phase, larger studies using modified stimulation parameters and longer open-label periods may validate the use of nVNS in migraine therapy; a study with a 9-month open-label period is currently planned.

Author Contributions

This study was sponsored by electroCore, LLC. Professional writing and editorial support (i.e., technical editing, copyediting, preparation of tables and figures, and clerical assistance) from MedLogix Communications, LLC, funded by electroCore, LLC, was based on author direction throughout draft development and revisions. Data analysis support from NAMSA was funded by electroCore, LLC. Dr. Stephen D. Silberstein, Dr. Peter J. Goadsby, Eric J. Liebler, and Kristy A. Simmons contributed to the EVENT study design and provided detailed input into the development of the manuscript. Stefanie Doelas is responsible for drafting/revising the manuscript for content, including medical writing for content. All primary investigators were involved in participant recruitment and treatment for the EVENT study. All authors participated in data collection, interpretation, and validation. Kristy A. Simmons, Eric J. Liebler, and NAMSA were involved in data analysis. All authors reviewed, critiqued, and contributed to revision of the manuscript content and provided approval of the final manuscript draft to be submitted to Neurology®.

The corresponding author, Dr. Stephen D. Silberstein, had full access to all the study data and had final responsibility for the decision to submit the manuscript for publication.

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Disclosure

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Comment: Noninvasive vagus DBS—Preliminary study encouraging for chronic migraine

Headache disorders are the most common, among the most disabling, and the most treatable of all neurologic conditions. Despite numerous available therapies, patients with refractory migraine, cluster headache, and other headache types are in need of effective treatment. Neurostimulation, utilized for decades to treat pain originating from the spinal cord, is gaining momentum for treating cephalalgic pain. Surgical procedures investigated to date include occipital and supraorbital nerve stimulation for migraine and cluster, deep brain stimulation (DBS) of the posterior hypothalamus, and sphenopalatine ganglion (SPG) stimulation for chronic cluster. While DBS is fraught with surgical complications, some serious, both DBS and SPG stimulation showed a long-term reduction in cluster attack frequency, suggesting a disease-modifying effect. Transcutaneous supraorbital nerve stimulation and transcranial magnetic stimulation are available noninvasive options.

Noninvasive vagus nerve stimulation (nVNS) was studied in a small (n = 27) open-label study of acute migraine treatment, showing modest benefit (22% pain freedom at 2 hours for moderate to severe attacks, 38% for mild attacks), without cardiac side effects. EVENT was a pilot study of nVNS to assess safety, tolerability, efficacy, and satisfaction data for the prevention of chronic migraine. Tolerability was similar to sham treatment. The study was underpowered to assess efficacy, with no difference between treatment groups at the end of the randomized phase. Among those participants who completed the open-label phase of the trial, there was a greater reduction in headache days, similar to previous stimulation studies.

Further studies with a larger sample size and a longer treatment phase are needed to determine the role of nVNS in the therapy of migraine. An effective noninvasive neurostimulation device is an attractive treatment alternative for patients with medically refractory migraine, and for those who are unable to take currently used oral prophylactic treatments.


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