

Review of Evidence on Noninvasive Vagus Nerve Stimulation for Treatment of Migraine: Efficacy, Safety, and Implications

By Mkaya Mwamburi, MD, PhD; Andrew T. Tenaglia, BA; Eric J. Leibler;
and Peter S. Staats, MD, MBA

The FDA cleared gammaCore (noninvasive vagus nerve stimulator [nVNS]; electroCore Medical, LLC, Basking Ridge, NJ) for the acute treatment of migraine in the United States in January 2018.¹ GammaCore was previously approved for the treatment of episodic cluster headache in 2017 and has 5 Conformité Européenne marks for multiple indications, including one for primary headaches.² Migraine is defined as a recurrent headache disorder manifesting in attacks lasting 4 to 72 hours, with or without aura.³⁻⁵ It may be episodic or chronic, depending on the number of headache days experienced in a month.³⁻⁵ Approximately 15% of the population in the United States suffer from migraine, accounting for 35 million individuals.³⁻⁵ Additionally, migraine is responsible for a substantial and disproportionate amount of clinical and economic burden.⁴⁻⁶ Although numerous medications are approved and used for acute treatment of episodic and chronic migraine, such as nonsteroidal anti-inflammatory drugs (NSAIDs), opiate-based analgesics, triptans, and ergotamine tartrate, among others, an estimated 3 million patients are dissatisfied with the available treatment options.⁴⁻⁸ Outside the United States, gammaCore is used for multiple indications.^{9,10} Prior to its FDA clearance, gammaCore has been shown to be safe and effective across a range of migraine populations in both the United States and Europe. Various treatment strategies have been evaluated with clinical, safety, and quality of life outcomes at varying study durations. A review of the evidence is critical when evaluating this newly approved treatment for migraine, to inform and update practice guidelines and reimbursement policies.

We performed a qualitative review of the literature, focusing on available evidence regarding the efficacy and safety of gammaCore in migraine. The purpose was to understand data highlighting the potential long-term benefits of gammaCore in managing patients with migraine, particularly those that remain dissatisfied by the available medications.

Methods

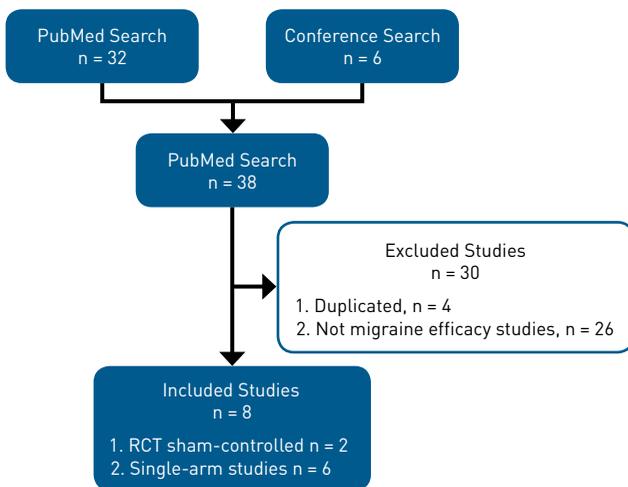
In addition to reviewing literature related to the efficacy and safety of gammaCore in the treatment of migraine, we evaluated studies

ABSTRACT

GammaCore was cleared by the FDA for the acute treatment of episodic migraine and episodic cluster headache and has 5 Conformité Européenne marks. Data indicate that gammaCore treatment is both safe and effective as an acute treatment for migraine. Current reimbursement policies need to be updated based on the growing body of evidence to reflect the established status of gammaCore that is no longer experimental. GammaCore provides substantial value to patients and to payers for consideration for pay-for-performance health coverage strategies and policies.

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For author information and disclosures, see end of text.

FIGURE 1. PRISMA Diagram of Study Attrition

RCT indicates randomized controlled trial.

that assessed the effects of gammaCore on various outcomes through quantitative and qualitative analysis of the evidence.

Sources of Evidence

Evidence from the following sources were reviewed:

1. Research published before January 31, 2018, in English, that focused on efficacy and safety of gammaCore for treatment of migraine in humans.
 - a. The search strategy was defined by search terms in PubMed using key terms and their respective variations and Medical Subject Headings equivalents for “noninvasive vagus nerve stimulation,” “nVNS,” or “gammaCore.”
 - b. Primary studies were excluded if they were:
 - i. Non-migraine studies
 - ii. Focused on other nVNS (non-gammaCore)
 - c. Studies identified in bibliographies of qualifying research studies
2. Studies presented from 2015 to 2017 at conferences focused on gammaCore treatment or effectiveness of migraine, specifically. ElectroCore provided a complete list of publications, abstracts, and posters presented at conferences, including those of the American Headache Society, American Academy of Neurology, European Headache Federation, and European Headache and Migraine Trust International Congress.

Study Selection

All publications and conference presentations on gammaCore were reviewed. The search yields from PubMed and conference proceedings were combined, and duplicate studies were removed. If studies were published as full-text peer-reviewed journal articles and presented in conference proceedings, the most recent cumulative information of the studies from all sources were included.

Qualitative Analysis

Data were analyzed qualitatively in the following categories:

1. Randomized trials
2. Single-arm studies of gammaCore and case series

Results

The PubMed search yield was 32 studies; the search from conferences was 6 studies. Of the total of 38 studies, 30 were rejected (4 were duplicates and 26 were non-migraine studies). Of the 8 qualifying studies, 2 were sham-controlled randomized trials, 3 were observational studies about patients with migraine, and 3 were observational studies of patients with migraine.¹¹⁻¹⁸ Study attrition is shown in the PRISMA diagram (see [Figure 1](#)).

Randomized Trials

Two sham-controlled randomized trials were reported, evaluating efficacy and safety of gammaCore in the treatment of migraine.

Trial Designs

The prospective study of nVNS for the acute treatment of migraine (PRESTO) and the noninvasive neurostimulation for the prevention of chronic migraine (EVENT) trial are prospective, double-blind, sham-controlled, randomized trials with optional open-label extension phases.¹⁶ PRESTO evaluated the superiority of gammaCore plus standard of care (SOC), compared to SOC alone, in the acute treatment in patients with episodic migraine in 10 sites in Italy between January 2016 and March 2017. Patients in the trial remained on their migraine medications or SOC but were not allowed to start new prevention medications during the trial period. In PRESTO, patients with 15 headache days or fewer per month were evaluated in a 4-week run-in period, a 4-week double-blind randomization phase, and a 4-week open-label extension phase in which patients who completed the double-blind phase optionally received additional gammaCore in addition to SOC treatment.

The EVENT study evaluated efficacy of gammaCore plus SOC in comparison with SOC alone in preventive treatment of patients with chronic migraine.¹⁵ EVENT was a prospective, multicenter, open-label, randomized, controlled trial in patients with 15 or more headache days per month that was conducted in 6 tertiary care headache centers in the United States between October 2012 and April 2014. Patients were randomized to receive gammaCore plus SOC versus SOC alone for 2 months, followed by an open-label phase of gammaCore plus SOC treatment for 6 months.

In both trials, patients were randomized to gammaCore, which produces a proprietary low-voltage electrical signal comprising a 5 kHz sine wave burst lasting for 1 millisecond (5 sine waves, each lasting 200 microseconds). Such bursts repeated once every 40 milliseconds (25 Hz) generating a 24 V peak voltage and 60 mA peak output current.¹⁹ The sham device produced a low-frequency

(0.1 Hz) biphasic signal that did not stimulate the vagus nerve or generally cause muscle contraction.

Trial Results

In both trials, the mean age of patients was approximately 39 years, mostly female (at least 74%). Patients reported at baseline that the average number of headaches per month was approximately 6 for the PRESTO study, and approximately 21 for the EVENT study. Baseline characteristics for PRESTO and the EVENT studies are shown in **Table 1**.¹¹⁻¹⁸

PRESTO consisted of a study population of 243 episodic patients with migraine for acute treatment (gammaCore, n = 120 vs sham, n = 123). For the first treated migraine attack, the pain-free rate was higher in gammaCore than in sham patients at 30 minutes (gammaCore, 12.7% vs sham, 4.2%; P = .012) and 60 minutes (gammaCore, 21.0% vs sham, 10.0%; P = .023). It was not higher at 120 minutes

in gammaCore than in sham patients (gammaCore, 30.4% vs sham, 19.7%; P = .067). A repeated-measures test across the 30-, 60-, and 120-minute findings demonstrated superiority of gammaCore over sham patients for the pain-free outcome with an odds ratio of 2.3 (95% CI, 1.2-4.4, P = .012). Mild or no pain responder rates and reductions in pain score are shown in **Table 2**.¹¹⁻¹⁸ The safety profiles for gammaCore and sham were similar. All device-related adverse events (AEs) reported were mild and transient with no serious device-related AEs reported. Twenty-two patients (18%) reported at least 1 AE in the gammaCore group, compared with 23 (18%) in the sham group. The number of patients reporting at least 1 device-related AE was 7 (6%) in the gammaCore group, compared with 10 (8%) in the sham group.

In the EVENT study, 59 chronic patients with migraine for prevention treatment formed the study population (gammaCore, n = 30 vs sham, n = 29). The mean change in number of headache days

TABLE 1. Study and Baseline Patient Characteristics of the Included Studies¹¹⁻¹⁸

Study, Year, Author	• Study Design, Country • Treatment Strategy Used for Migraine Population	Treatment (n)	Age in Years, Mean ± SD	n (%) Females	Attacks in Past 4 Weeks, Mean ± SD	Headache Days in Past 4 Weeks, Mean ± SD	Acute Medications Use, Days/m Mean ± SD	Prevention Medications Use, n (%)
Sham-controlled RCTs								
PRESTO, 2018, Tassorelli	• RCT, sham-controlled, multicenter, Italy • Acute treatment for episodic migraine	gammaCore + SOC (120)	38.8 ± 11.0	95 (79.2)	5.4 ± 1.7	6.3 ± 1.7	42 (35)	5.6 ± 1.7
		Sham + SOC (123)	39.6 ± 11.8	91 (74.0)	5.3 ± 2.3	6.2 ± 3.1	35 (28.5)	5.3 ± 1.7
EVENT, 2016, Silberstein	• RCT, sham-controlled, multicenter, Italy • Preventive treatment for chronic migraine	gammaCore + SOC (30)	40.5 ± 14.2	26 (87)	NR	20.5 ± 5.0	NR	NR
		Sham + SOC (29)	38.8 ± 11.1	27 (93)	NR	22.3 ± 4.9	NR	NR
Open-label studies								
2017, Barbanti	• Open-label, Italy	gammaCore + SOC (50)	43.3 ± 11.3	40 (80.0)	NR	15.4 ± 5.6	NR	NR
2014, Goadsby	• Open-label, multicenter, US	gammaCore + SOC (30)	39 (median)	25 (83.3)	NR	NR	NR	NR
2014, Rainero	• Open-label, Italy	gammaCore + SOC (15)	49.9 ± 15.4	14 (93.3)	NR	NR	NR	NR
Menstrual-related migraine, migraine in adolescents, and migraine with sleeping disorders								
2016, Grazzi	• Open-label, Italy • Menstrual-related migraine	gammaCore + SOC (56)	40.2 ± 1.0	56 (100.0)	NR	7.2 ± 0.7	20 (100)	20 (100)
2015, Kinfe	• Open-label, Germany • Migraine + sleep disorder	gammaCore + SOC (20)	53.1 ± 11.5	16 (80.0)	NR	15.0 ± 4.5	20 (100)	20 (100)
2016, Grazzi	• Pilot, Italy • Acute treatment in adolescents	gammaCore + SOC (8)	16.1 ± 1.8	6 (75)	NR	5.4 ± 1.3	NR	NR

NR indicates none reported; RCT, randomized controlled trial; SOC, standard of care; SD, standard duration; US, United States.

TABLE 2. Summary of Study Outcomes¹¹⁻¹⁸

Study, Author, Year	Outcome 1						Outcome 2					
	Pain-free response rate, %			P			Mild or no pain response rate, %			P		
	30 min	60 min	120 min	30 min	60 min	120 min	30 min	60 min	120 min	30 min	60 min	120 min
PRESTO, 2018, Tassorelli												
gammaCore (120)	12.7	21.0	30.4	.01	.02	.067	26.7	35.8	40.8	.14	.05	.03
Sham (123)	4.2	10.0	19.7				18.7	24.4	27.6			
EVENT, 2016, Silberstein	Change in number of headache days/month at 2 months			P			Response for ≥50% reduction in headache days at 2 months			Response rate (95% CI); P		
gammaCore (30)	-1.4 (-3.7 - 0.70)			.56			10%			NR		
Sham (29)	-0.2 (-1.5 - 1.1)						0%					
2017, Barbanti	Response to treatment by patients, pain free n (%)			P			Response to treatment by patients, pain relief n (%)			P		
	1 hour	2 hours		1 hours	2 hours		1 hour	2 hours		1 hour	2 hours	
gammaCore (50)	17 (35.4)	19 (39.6)		—	—		27 (56.3)	31 (64.6)		—	—	
2014, Goadsby	Patients: Pain free at 2 hours		Patients: Pain relief at 2 hours		Patients: Mild pain to pain free at 2 hours		Attacks: Pain free at 2 hours					
gammaCore (30)	4/19 (21%)		9/19 (47%)		5/8 (63%)		12/54 (22%)					
2014, Rainero	Attacks: Pain free at 2 hours		Average pain reduction at 2 hours (0-3 scale)		Rescue medication use reduction from 100% at 6 months							
	121/362 (33.4%)		-0.56		67/362 (18.5%)							
2016, Grazzi Menstrual	Change in migraine days per month			P			Proportion with ≥50% mean number of migraine days			P		
	-2.40			<.001			39%			<.001		
2015, Kinfe Sleep disorder	Change in VAS			P			Change in headache days per month			P		
	-3.70			<.001			-5.8			<.001		
2016, Grazzi Adolescents	Attacks: pain free at 1 hour		Attacks: Mild pain or pain free at 1 hour		Mean change in pain score: pain free		Mean change in pain score: mild pain					
	17/44 (39%)		21/44 (48%)		-2.1 (-100%)		-2.5 (-66%)					

(continued »)

Outcome 3			Outcome 4				Outcome 5					
Percentage change in pain score			P			Treatment response for ≥50% of attacks, pain free (%) at 120 min	P		Treatment response for ≥50% of attacks, mild or no pain (%) at 120 min	P		
30 min	60 min	120 min	30 min	60 min	120 min							
-18.1	-25.4	-34.8	.06	.03	<.01	32.4	.02	47.6	.03			
-5.2	-7.7	-5.4				18.2		32.3				
Difference in number of headache days/month at 4, 6, and 8 months			P			Response for ≥50% reduction in headache days						
4 months	6 months	8 months	4 months	6 months	8 months	2 months	4 months	6 months	8 months			
-3.7	-6.1	-8.0	<.05	<.01	<.01	4/44	7/32	10/26	7/15			
—	—	—				9.1	21.9	38.5	46.7			
Response to treatment by attacks, pain free n (%)			P		Response to treatment by attacks, pain free n (%) ^c							
1 hour	2 hours		1 hour	2 hours	1 hour	2 hours	1 hour	2 hours				
23 (17.6)	30 (22.9)		--	--	50 (38.2)	67 (51.1)	—	—				
Attacks: Pain relief at 2 hours		Attacks: Mild pain to pain free at 2 hours		Treatment response for ≥50% of attacks, pain free (%)		Symptom alleviation during gammaCore treatment at 2 hours						
23/54 (43%)		10/26 (38%)		12/31 (39%)		Nausea	Photophobia	Phonophobia				
						11/29 (38%)	16/53 (30%)	17/33 (52%)				
Mean analgesic use, times per month			P			Change in HIT-6 score		P		Change in MIDAS score/MIDAS grade		P
-3.3			<.001			-3.10		<.001		-11.9/-0.3		<.001/.008
Average time to achieve pain relief			P			Change in MIDAS score/MIDAS grade		P		Change in BDI score		P
31.75			.002			-10.85/-0.75		.01/<.01		-6.5		<.001

BDI indicates Beck Depression Inventory; HIT, headache impact test; min, minutes; VAS, pain intensity score; MIDAS, migraine disability assessment; NR, no response; PSQI, Pittsburgh Sleep Quality Index.

in the gammaCore versus sham groups were -1.4 (95% CI, -3.7 to 0.77 ; $P = .44$) versus -0.2 (95% CI, -1.5 to 1.1 ; $P = .72$). Persistent prophylactic gammaCore use was associated with continued reductions in the number of headache days. After the open-label phase, participants initially assigned to gammaCore had a mean change from a baseline of -2.5 (95% CI, -5.0 to -0.04 ; $P = .06$) and -3.6 (95% CI, -6.3 to -0.87 ; $P = .02$) after 6 and 8 months of treatment. The mean changes in the number of headache days analyzed without last observation carried forward imputation from baseline at months 4, 6, and 8 were -3.7 , -6.1 , and -8.0 headache days respectively in the gammaCore group (month 4, $P < .05$; months 6 and 8, $P < .01$). Eight months from baseline, the mean change for controls during the gammaCore extension phase was -6.0 headache days ($P < .05$), representing 6 months of gammaCore use. The proportion of participants from the gammaCore group that had a $\geq 50\%$ response at month 2 was 10.0%, though no controls experienced a $\geq 50\%$ response.

The safety profiles for gammaCore and sham were similar, and all device-related AEs reported were mild and transient, with no serious device-related AEs reported. A total of 17 participants reported at least 1 AE in the gammaCore group, with 1 participant reporting severe intensity. In the sham group, of 16 patients individuals experiencing AEs, 4 reported severe intensity.

Nonrandomized Studies

Barbanti et al (2015) conducted a study for the acute treatment of migraine attacks in 50 patients (36 had high frequency episodic migraine; 14 had chronic migraine).¹⁷ GammaCore led to pain relief after 1 hour in 56.3% of patients, with 35.4% becoming pain free. After 2 hours, 64.6% reporting pain relief, with 39.6% being pain free.¹⁷ Of the 131 attacks treated in the 50 patients, gammaCore led to pain relief after 1 hour in 38.2% of patients, with 17.6% being pain free. At 2 hours, gammaCore led to 51.1% reporting pain relief, with 22.9% being pain free. Goadsby et al (2014) also conducted a study for acute treatment of migraine attacks in 30 patients asked to treat up to 4 attacks with gammaCore. Results showed that gammaCore led to pain relief after 2 hours from moderate to severe pain in 47% of patients, with 21% being pain free.¹¹ In 54 attacks treated, gammaCore led to pain relief after 2 hours from moderate to severe pain in 43% of patients, with 22% being pain free. In 26 attacks, 38% reported to being pain free after 2 hours from mild pain. Of the 31 patients who treated 3 or 4 attacks, 39% achieved $\geq 50\%$ response rate. In addition, gammaCore treatment resulted in alleviation of nausea, photophobia, and phonophobia in improved function disability scores. Other findings showed that gammaCore resulted in 33.4% of patients who experienced attacks becoming pain free after 2 hours, with a mean reduction in pain scores of 0.56 (on a 0-3 scale) and reduction in use of rescue medication to 18.5% of patients from 100% at baseline.¹⁸

Grazzi et al (2016) enrolled 56 patients with menstrual migraine (9%) or menstrually related migraine (91%) to receive prophylactic

gammaCore adjunctive to standard therapy.¹² GammaCore resulted in a mean reduction of number of headache days per month, from 7.2 to 4.7. The proportion of patients reducing their headache days per month by $\geq 50\%$ was 39%, and the number of times analgesics were used per month was reduced by 3.3. In addition, gammaCore resulted in mean changes in 6-item Headache Impact Test score (-3.1), and Migraine Disability Assessment score ([MIDAS]; -11.9) in pain intensity (-0.5).

Kinfe et al (2015) enrolled 20 patients to assess preventive and acute treatment with gammaCore in patients with treatment-refractory episodic or chronic migraine with migraine-associated sleep disturbances, disabilities, or depressive symptoms confirmed by a multidisciplinary pain board.¹⁴ All patients in the study were considered refractory to prophylactic treatment, having previously failed 4 or more classes of medications (ie, β -blockers, anticonvulsants, tricyclic antidepressants, and calcium channel blockers) and behavioral therapy. GammaCore resulted in a mean reduction in pain intensity visual analog scale score (-3.7). The number of headache days per month reduced by prophylactic treatment was 5.8, while the average time to achieve pain relief during acute treatment was 31.73 minutes. GammaCore also resulted in mean reductions in MIDAS (-10.85), Beck Depression Inventory for depressive symptoms (-6.5), and Pittsburgh Sleep Quality Index daytime dysfunction scores for sleep disorder (-0.75).

Grazzi et al (2016) enrolled 8 patients aged between 13 to 18 years to assess acute treatment with gammaCore in adolescent patients with migraine with or without aura experiencing 5 to 8 migraine days per month.¹³ GammaCore resulted in 48% of 44 attacks treated in the study achieving mild pain or pain free status in 1 hour with 39% being pain free. The mean reduction in pain intensity score was -2.1 among those who achieved pain free status and -2.5 intensity pain score for those who achieved mild pain status. Study outcomes are shown in Table 2 and the safety findings, implications, and interpretations of the findings are shown in Table 3.¹¹⁻¹⁸

Discussion

The findings of this review include results from 2 double-blind, sham-controlled randomized trials (PRESTO and EVENT studies) and 6 single-arm studies demonstrating the effects of gammaCore when used adjunctively with SOC treatments acute and/or prophylactic treatment of episodic and chronic migraine headaches. PRESTO demonstrated superiority of gammaCore over SOC alone in the rapid response to acute treatment of migraine attacks. It also significantly reduced the pain intensity across 30-, 60- and 120-minute timepoints and showed patients consistently responded better ($> 50\%$ response rates).¹⁶ The findings from PRESTO provided the evidence to support the FDA clearance in January 2018 for gammaCore during acute treatment of pain associated with migraine in the United States.¹ Although the EVENT

TABLE 3. Safety and Implications of Study Findings¹¹⁻¹⁸

Study, Year, Author	Study Design, Country	Safety Findings	Overview of Study Findings and Implications
PRESTO, 2018, Tassorelli	RCT, sham-controlled, multicenter, Italy	Acute nVNS therapy demonstrated a highly favorable safety and tolerability profile. Participants reported no SAEs during the study.	<ol style="list-style-type: none"> 1. Overview: <ol style="list-style-type: none"> a. Findings demonstrate rapid efficacy of nVNS for the acute treatment of episodic migraine and confirm its practicality and strong safety and tolerability profile USPSTF Evidence level: Level I 2. Implications and interpretations: <ol style="list-style-type: none"> a. nVNS consistent efficacy, safety and tolerability, established over multiple studies, make it an attractive option for early and frequent use for patients with migraine b. nVNS may be used in conjunction with existing treatments without drug interactions or as monotherapy and reducing the need for rescue medications c. Main evidence used for FDA review and approval process
EVENT, 2016, Silberstein	RCT, sham-controlled, multicenter, United States	The tolerability profile of nVNS was satisfactory and similar to that of sham treatment. AEs were mild or moderate and transient.	<ol style="list-style-type: none"> 1. Overview: <ol style="list-style-type: none"> a. 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. 2. USPSTF Evidence level: Level I 3. Implications and interpretations: <ol style="list-style-type: none"> a. nVNS is a highly feasible, well-tolerated, and convenient therapy b. Prophylaxis for chronic migraine c. Longer-term use in treatment responders would be reflective of clinical practice. d. Evidence represents good example for long-term performance-based value structure e. Larger studies or real-world data may validate the use of nVNS in migraine therapy f. Cited as current evidence in payer policy documents
2017, Barbanti	Open-label, Italy	No major adverse events were reported. All patients considered nVNS treatment to be safe.	<ol style="list-style-type: none"> 1. Overview <ol style="list-style-type: none"> a. The data confirmed that nVNS is well tolerated and safe and is associated with treatment satisfaction and therapeutic adherence 2. USPSTF Evidence level: Level II - 1 3. Implications and interpretations: <ol style="list-style-type: none"> a. Findings from this study expanded the body of clinical evidence on nVNS to the HFEM/CM population whose pain is difficult to manage b. From a risk-benefit perspective, nVNS therapy achieved pain relief without serious adverse effects, which may decrease patients' reliance on migraine medications and, in turn, lower the risk of medication overuse
2014, Goadsby	Open-label, multicenter, United States	There were no unanticipated AEs. Of anticipated AEs, all were judged mild or moderate.	<ol style="list-style-type: none"> 1. Overview <ol style="list-style-type: none"> a. Data demonstrated a high pain-free rate at 2 hours in patients with a baseline of moderate or severe intensity pain b. Device was well tolerated with no unanticipated, serious or severe AEs 2. USPSTF Evidence level: Level II - 1 3. Implications and interpretations: <ol style="list-style-type: none"> a. Patients with migraine needed more and better-tolerated therapies, and nVNS had significant potential to mitigate that unmet need b. Cited as current evidence in payer policy documents
2014, Rainero	Open-label, Italy	AEs were mild and transient.	<ol style="list-style-type: none"> 1. Overview <ol style="list-style-type: none"> a. Pain-free response was observed in approximately one third of treated patients b. All the patients halted the drug of abuse and significantly reduced the consumption of antimigraine drugs 2. USPSTF Evidence level: None (unpublished) 3. Implications and interpretations: <ol style="list-style-type: none"> a. nVNS could be a safe and efficacious treatment and associated with reduced medication use

(continued)

TABLE 3. (Continued) Safety and Implications of Study Findings¹¹⁻¹⁸

Study, Year, Author	Study Design, Country	Safety Findings	Overview of Study Findings and Implications
2016, Grazzi Menstrual	Open-label, Italy Menstrual-related Migraine	There were no safety concerns during the study. AEs were mild or moderate and were transient in nature. No serious AEs occurred.	<ol style="list-style-type: none"> Overview <ol style="list-style-type: none"> Findings suggested that prophylaxis with nVNS was effective and reduced the number of MM/MRM days and acute analgesic use without adding treatment-related safety concerns USPSTF Evidence level: Level II - 1 Implications and interpretations: <ol style="list-style-type: none"> Study also expanded the body of evidence on MM/MRM, for which there are no specifically approved therapies. As the first neuromodulation technique evaluated in patients with MM/MRM, nVNS offered an important new option for effectively treating the condition while mitigating the monthly peri-menstrual AE burden and potential complications of pharmacologic medications
2015, Kinfe Sleep disorder	Open-label, Germany Migraine + sleep disorder	AEs were mild or moderate and were transient in nature.	<ol style="list-style-type: none"> Overview <ol style="list-style-type: none"> Findings suggested that nVNS therapy in patients with treatment-refractory migraine was associated with significant reductions in migraine attack frequency, pain intensity, and duration There were clinically meaningful improvements in migraine-associated disability, depression, and sleep quality USPSTF Evidence level: Level II - 1 Implications and interpretations: <ol style="list-style-type: none"> gammaCore worked in patients considered refractory to prophylactic treatment Treatment may help treat migraine-related comorbidities
2016, Grazzi Adolescents	Open-label pilot, Italy Acute treatment in adolescents	Patients did not report any device-related AEs and there were no safety concerns or discontinuations	<ol style="list-style-type: none"> Overview <ol style="list-style-type: none"> Use of nVNS in 8 adolescents was safe, well tolerated, and practical for the treatment of migraine nVNS treatment when pain was milder in intensity was more likely to result in a pain-free outcome at 1 hour USPSTF Evidence level: Level II -3 Implications and interpretations: <ol style="list-style-type: none"> Results of this pilot trial were promising and comparable to open-label data from other sensitive patient populations Findings were consistent with results of other migraine studies and particularly relevant given the rapid onset and short duration of attacks that occur in adolescents

AE indicates adverse event; CM, chronic migraine; HFEM, high frequency episodic migraine; MM, menstrual migraine; MRM, menstrual-related migraine; nVNS, non-invasive vagus nerve stimulation; RCT, randomized controlled trial; SAE, significant adverse event; USPSTF, United States Preventive Services Task Force.

study did not meet its primary endpoint during the randomization phase, the extension phase of the study demonstrated the continued increase in effect of gammaCore as a prophylactic treatment beyond 6 months of use, particularly for those who self-selected to keep using gammaCore.¹⁵ Findings from the other single-arm studies support the findings from PRESTO and EVENT. They also demonstrate rapid pain relief during acute treatment and reduction in up to an average of 8 migraine days per month after 8 months of follow-up during prophylactic treatment of chronic migraineurs.^{11,17,18} In addition, there is improvement in numerous QOL measures to improve the symptoms accompanying migraine headaches. Another important and consistent finding in the studies is that they demonstrate that gammaCore is safe to use and that they all reported mild and transient AEs. In the randomized trials, even for the cluster headache, the AE rates were similar to the comparator sham or SOC control populations.¹⁹⁻²¹

In addition to the clearance for migraine and episodic cluster headache by the FDA in the United States, gammaCore has regulatory approval for the acute and prophylactic treatment of migraine and cluster headache in Australia, Brazil, Canada, Colombia, the European Union (EU), India, Malaysia, New Zealand, and South Africa.⁹ In EU, gammaCore is a class IIa CE mark-approved medical device for the treatment of primary headaches, including migraine and cluster headaches, depression, anxiety, epilepsy, bronchoconstriction, and gastric motility disorders. The efficacy and performance of gammaCore as a nVNS in significantly reducing migraine attack intensity, duration, and adjunct medication use in acute treatment and in reducing headache days per month in prophylactic treatment is supported by numerous robust mode of action studies of gammaCore.²²⁻²⁹

Studies have shown that patients with primary headaches often have multiple comorbidities with significantly higher healthcare

costs compared with patients with no reported comorbidities or non-headache patients.^{30,31} In 1 study, gammaCore treatment for primary headache was associated with reductions in general practitioner appointments, referrals to specialists, and with improvement in QOL.³² GammaCore is beneficial in patients with migraine dissatisfied with currently available treatments. It safely improves outcomes and quality of life, while reducing reliance on other medications and decreases healthcare utilization.

In addition to being safe and effective, gammaCore is easy to use.¹⁹ It is simple for patients to apply without assistance, prophylactically or during an attack. Because the delivery of treatment doses is measured out, doses cannot be wasted.³³ GammaCore Sapphire is a Bluetooth-enabled, electronic device.⁹ Treatment delivery, adherence, and performance are easy to monitor.⁹ The ability to seamlessly communicate with other devices, such as smartphones or laptops, for passive or prompted data capture, aligns well with the growing trends towards performance-based coverage. A recent study of over 550,000 patients in Denmark followed over 20 years showed an association between migraine and increased risk of myocardial infarction, ischemic and hemorrhagic strokes, venous thrombosis, and atrial fibrillation, suggesting migraine could be an important risk factor.³⁴ This successful and consistent treatment of migraine is critical. These value attributes for patients translate to value for payers and should impact current reimbursement policies.

Patients with migraine who experience 2 or more headache days per month and remain dissatisfied with their current treatment are the best candidates to try gammaCore. Patients and their respective providers who feel the response to gammaCore are adequate in controlling their headaches are most likely to benefit in reducing their overall healthcare utilization needs and, ultimately, their cost burden. The subgroup represents approximately 7% of the migraine population in the US (2 million sufferers).⁶

New evidence is emerging on the efficacy of monoclonal antibodies that serve as calcitonin gene-related peptide receptor inhibitors (erenumab and fremanezumab), and regarding the long-term use of onabotulinumtoxinA.³⁵⁻³⁷ It is also important to understand the optimal role for gammaCore in the subgroup of patients with migraine in relation to the medications. The emerging evidence demonstrates the efficacy in prophylactic use for these 3 agents: erenumab in episodic migraine, fremanezumab, and onabotulinumtoxinA in chronic migraine. These have not been tested or indicated for the acute treatment of migraine domain. In addition, the levels of efficacy demonstrated are similar and comparable to the corresponding effects seen in gammaCore. Erenumab, in episodic patients with migraine, resulted in mean reduction in headache days between 3.2 and 3.7, depending on the dose tested. In comparison, when gammaCore was tested for prevention in episodic patients with migraine, the mean reduction in headache days was 5.7, even though these patients with sleeping disorders

considered refractory and prophylactic treatment, having previously failed 4 or more classes of medications and behavioral therapy.¹⁴ In chronic patients with migraine, fremanezumab resulted in a mean reduction in headache days of between 4.3 and 4.6, after 3 months, depending on the injection frequency tested. OnabotulinumtoxinA, also in chronic patients with migraine, resulted in mean reduction in headache days of 9.2 after 11 months. In comparison, when gammaCore was tested for prevention in chronic patients with migraine, reduction of headache days was 5.9 at 3 months. In the EVENT study extension phase, the mean reduction in headache days was 3.7 at 4 months and 8.0 after 8 months.^{14,15}

GammaCore can be used for acute attacks in patients on prophylactic treatment.^{14,16} Finally, gammaCore is relatively inexpensive and was more cost-effective in comparison to SOC in the acute and preventive treatment of cluster headache.^{38,39} A recent study has also shown gammaCore to be more cost saving for acute treatment of episodic migraine. Based on the growing body of evidence on gammaCore in the headache domain, reimbursement policies for payers in the United States on nVNS coverage explicitly should be updated accordingly, and payers should consider transforming the evidence status from “experimental and investigational” to “established.”⁴⁰⁻⁴²

As with any review, there are strengths and limitations. Most evidence included in the literature review is peer-reviewed research, except 1 study that has not yet been published in the peer-reviewed literature. The new evidence presented in this review is from robust, high-quality, research designs data. The efficacy of gammaCore in acute treatment for both episodic and chronic migraine has demonstrated the value of gammaCore. The outcomes of the trial were clinically relevant and appropriately measured. This is the first review on gammaCore for migraine headache. It provides evidence and discusses the treatment gap for patients with migraine and the value structure for patients and payers. There is further need to collect real-world data that is specific to patients suffering from episodic and chronic migraine regarding gammaCore use via a registry to monitor usage. Performance measurements will shape the future for these patients and optimize their care. Randomized trials for gammaCore in preventive treatment with adequate sample size and follow-up duration are also needed. Additionally, review and analyses of claims data to evaluate long-term outcomes in relation to utilization, cost, reimbursement burden, and the impact of comorbidities, will increase understanding of the value associated with gammaCore use beyond symptom relief. There is also a need to evaluate the cost-effectiveness of gammaCore for treatment of patients with migraine.

Conclusions

The use of gammaCore is supported by a growing body of evidence that demonstrates the value attributes for patients who suffer from migraine. GammaCore will also provide value to payers. Finally, there is sufficient evidence to support the need to further update and

modify current reimbursement policies to acknowledge the evidence that this therapy is no longer experimental or investigational. ■

Author Affiliation: electroCore, Inc, Basking Ridge, NJ (EJL, PSS, ATT); profecyINTEL, LLC, Bridgewater, NJ (MM).

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Address correspondence to: mkaya.mwamburi@profecyintel.com; peter.staats@electrocore.com; andrew.tenaglia@electrocore.com.

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