REPORT

Review of Non-Invasive Vagus Nerve Stimulation (gammaCore): Efficacy, Safety, Potential Impact on Comorbidities, and Economic Burden for Episodic and Chronic Cluster Headache

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In April 2017, the FDA cleared gammaCore (non-invasive vagus nerve stimulator [nVNS]; electroCore Medical, LLC, Basking Ridge, NJ) for the treatment of pain associated with episodic cluster headache (eCH) in the United States.[1] gammaCore has been available in Europe and other world regions since 2013 and is used for multiple indications, including cluster headache (CH) and migraine. CH, which may be episodic or chronic, is a type of primary headache that causes excruciating pain around the eyes that affects approximately 0.1% to 0.4% of individuals in the United States and Europe.[2,3] However, the disorder is responsible for a substantial and disproportionate amount of clinical and economic burden.[4,5] Only 1 other treatment, subcutaneous sumatriptan, is approved by the FDA for treatment of eCH in the United States. Other treatments for CH, such as intranasal zolmitriptan, ergotamine tartrate, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and NSAID-based combinations (eg, Excedrin), among others, are used off label.[6,7] High-flow oxygen is also used for treatment of acute attacks of CH. No treatment is approved by the FDA for prophylactic treatment of CH. However, similar to treatments used for acute attacks, many prophylactic treatments are used off label, including corticosteroids (eg, prednisone), verapamil, ergotamine tartrate, lithium, and divalproex sodium.[6,7] The effectiveness and reliability of previously used treatments for CH have been limited.[8]

Outside the United States, gammaCore is used for multiple indications. In the United Kingdom, for instance, the National Institute for Health and Care Excellence has provided guidance for gammaCore use for the prevention and acute treatment of migraine and CH.[9,10] In the 3 years prior to the FDA clearance of gammaCore in the United States, pivotal studies for gammaCore have cumulatively generated significant research data and new evidence for the efficacy of gammaCore in patients with CH. In addition, observational studies conducted in Europe provide evidence for the clinical and economic burden of CHs.[1,4-8,11-18] A review of new evidence, including data from recent pivotal trials, not captured in prior reviews, is critical when evaluating this newly approved treatment for eCHs in order to inform and update practice guidelines and reimbursement policies.

ABSTRACT

The FDA has cleared gammaCore (non-invasive vagus nerve stimulator [nVNS]) for the treatment of episodic cluster headache (eCH). With the exception of subcutaneous sumatriptan, all other treatments are used off label and have many limitations. The FDA approval process for devices differs from that of drugs. We performed a review of the literature to evaluate new evidence on various aspects of gammaCore treatment and impact. The ACute Treatment of Cluster Headache Studies (ACT1 and ACT2), both double-blind sham-controlled randomized trials, did not meet the primary endpoints of the trials but each demonstrated significant superiority of gammaCore among patients with eCH. In ACT1, gammaCore resulted in a higher response rate (RR) (RR, 3.2; 95% CI, 1.6-8.2; P = .014), higher pain-free rate for >50% of attacks (RR, 2.3; 95% CI, 1.1-5.2; P = .045), and shorter duration of attacks (mean difference [MD], –30 minutes; P <.01) compared with the sham group. In ACT2, gammaCore resulted in higher odds of achieving pain-free attacks in 15 minutes (OR, 9.8; 95% CI, 2.2-44.1; P = .01), lower pain intensity in 15 minutes (MD, –1.1; P <.01), and higher rate of achieving responder status at 15 minutes for ≥50% of treated attacks (RR, 2.8; 95% CI, 1.0-8.1; P = .058) compared with the sham group. The PREVention and Acute Treatment of Chronic Cluster Headache (PREVA) study also demonstrated that gammaCore plus standard of care (SOC) was superior to SOC alone in patients with chronic cluster headache (CH). Medical costs, pharmacy refills, and pharmacy costs were higher in patients coded for CH in claims data compared with controls with nonheadache codes. gammaCore is easy to use, practical, and safe; delivery cannot be wasted; and patients prefer using gammaCore compared with SOC. The treatment improves symptoms and reduces the need for CH rescue medications. Current US reimbursement policies, which predate nVNS and are based on expensive, surgically implanted, and permanent implanted vagus nerve stimulation (iVNS), need to be modified to distinguish nVNS from iVNS. gammaCore, cleared by the FDA in April 2017, provides substantial value to patients and also to payers. There is sufficient evidence to support the need to modify current reimbursement policies to include coverage for gammaCore (nVNS) for eCH.

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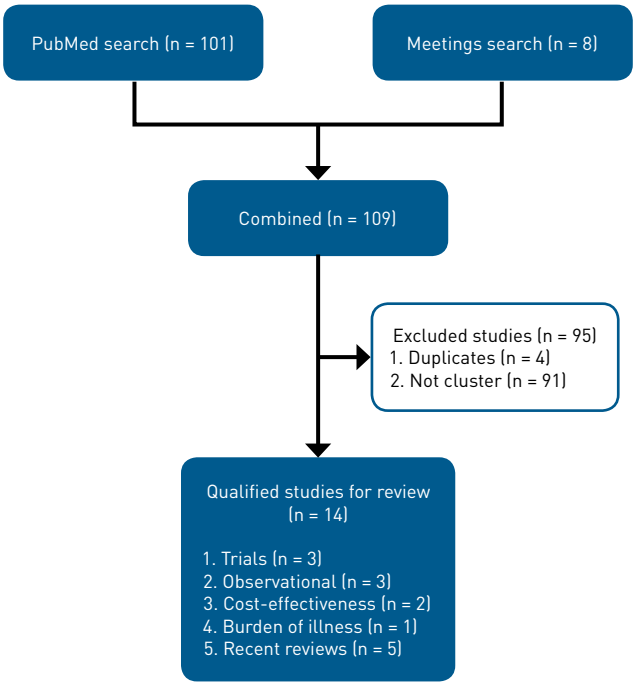
For author information and disclosures, see end of text.

FIGURE. PRISMA Diagram of Study Attrition



We perfomed a qualitative review of the literature that focused on available evidence regarding the efficacy, safety, and economic impact of gammaCore (nVNS) in episodic and chronic CH. The purpose was to understand the clinical and economic burden of CHs, highlighting the potential for longer-term benefits of adequately managing patients with CH.

Methods

We performed a review of literature, with qualitative analysis of the evidence related to the efficacy and effectiveness of gammaCore, including its safety and impact on quality of life in the treatment of eCH and chronic CH. We also evaluated the burden of illness of CHs.

Sources of Evidence

Evidence from the following sources were reviewed:

1. Research published before August 31, 2017, in English, that focused on gammaCore for treatment of CH 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:
      i. nVNS or gammaCore
   b. Primary studies were excluded if they were:
      i. Non-CH studies
      ii. Focused on other nVNS (nongammaCore)
      iii. Mixed-indication populations
   c. Reviews that included clinical applications for gammaCore (nVNS) published within 3 years of search date, including the role of gammaCore in current treatment landscape
   d. Studies identified in bibliographies of qualifying research studies
2. Recent studies, presented in 2014 to 2016 at conferences, that focused on gammaCore treatment, effectiveness, or burden of illness of CH specifically, or on primary headaches in general. electroCore provided a complete list of publications and abstracts/posters presented at conferences, including those of the American Headache Society, American Academy of Neurology, International Society of Pharmacoeconomics and Outcomes Research, and the Academy of Managed Care Pharmacy.

Study Selection

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

Qualitative Analysis

Data were analyzed qualitatively in the following categories:

1. Randomized trials
2. Observational studies on the potential impact of gammaCore and the burden of illness of CH specifically or of primary headaches in general
3. Cost-effectiveness studies of gammaCore treatment
4. Findings presented in recent reviews

Results

The PubMed search yield was 101 studies, while that from conferences was 8 studies. Of the total of 109 studies, 95 were rejected (4 were duplicate studies and 91 were non-CH studies). Of the 14 qualifying studies, 3 were randomized trials, 3 were observational studies, 2 were cost-effectiveness studies, 1 was a burden-of-illness study, and 5 were reviews or pooled analyses that included the clinical role of gammaCore. Study attrition is shown in the PRISMA diagram (**Figure**).

Randomized Trials

Three multicenter randomized trials were reported, evaluating efficacy, quality-of-life measures, and safety of gammaCore.[1,6,7]

Trial Designs

The ACute Treatment of Cluster Headache Studies (ACT1 and ACT2) were prospective, multicenter, double-blind, sham-controlled,

TABLE 1. Study and Baseline Patient Characteristics of the Included Studies[1,7]

Study, author, year	Country	Study design	Treatment (n)	Age in years, mean ± SD	% Males	% Episodic/ chronic	Duration of attack (minutes), mean ± SD	% Treatment use
ACT1, Silberstein SD et al, 2016	Multicenter, US	RCT, phase 3	gammaCore + SOC (73)	47.1 ± 13.5	80.8	68.5/31.5	86 ± 119	Triptans: 57.5; oxygen: 42.5; prophylaxis: 57.5
			Sham + SOC (77)	48.6 ± 11.7	87.0	66.2/33.8	64 ± 71	Triptans: 70.1; oxygen: 37.7; prophylaxis: 77.9
ACT2, FDA-Label, 2017	Multicenter, EU	RCT, phase 3	gammaCore + SOC (50)	43.9 ± 10.6	70.0	30.0/70.0	69.9 ± 68.7	Triptans: 74.0; oxygen: 54.0; verapamil: 36.0
			Sham + SOC (52)	46.9 ± 10.6	73.1	28.8/71.2	77.4 ± 76.9	Triptans: 65.3; oxygen: 59.6; verapamil: 44.2
Pooled ACT1 and ACT2, AAN, 2017	Multicenter, EU	Meta-analysis	gammaCore + SOC (124)	45.4 ± 12.4	75.8	64.5/35.5	--	Abortive: 92.7; preventive: 61.0
			Sham + SOC (129)	47.8 ± 11.2	81.4	51.2/48.8	--	Abortive: 96.8; preventive: 73.6
PREVA, Gaul C et al, 2016	Multicenter, EU	RCT, phase 3	gammaCore + SOC (48)	45.4 ± 11.0	71	0/100	95.2 ± 57.7	Medications: 90; oxygen: 67; verapamil: 52
			SOC only (49)	42.3 ± 11.0	67	0/100	103.3 ± 66.8	Medications: 90; oxygen: 69; verapamil: 53

AAN indicates American Academy of Neurology; EU, European Union; RCT, randomized controlled trial; SD; standard deviation; SOC, standard of care.; US, United States.

randomized trials with optional open-label extension phases. ACT1 and ACT 2 evaluated the superiority of gammaCore acute treatment in patients with both eCH and chronic CH who remained on their current CH medications or standard of care (SOC) (**Table 1**).[1,7] ACT1 was conducted across 20 US centers (ClinicalTrials.gov identifier: NCT01792817). Patients were evaluated in a double-blind randomization phase for 1 month or until 5 CH attacks were treated, and in an open-label phase in which patients who completed the double-blind phase optionally received 3 additional months of gammaCore treatment. ACT2, also a double-blind randomized trial with an open-label extension phase, was conducted in 9 European centers (ClinicalTrials.gov identifier: NCT01958125). A limitation of the ACT trials was that multiple attacks in an individual patient were treated as though they were independent events for 1 of the outcomes reported.

The PREVention and Acute Treatment of Chronic Cluster Headache (PREVA) study evaluated efficacy of gammaCore + SOC in comparison with SOC alone in preventive treatment of patients with chronic CH.[6,14] PREVA was a prospective, multicenter, open-label, randomized, controlled trial conducted at 10 European sites (ClinicalTrials.gov identifier: NCT01701245). Patients were evaluated in a 2-week run-in phase in which all participants received only their medications (SOC), followed by an open-label randomization phase for 1 month, followed by an open-label phase of gammaCore + SOC treatment for 1 month.

Trial Results

Study results for ACT1 and ACT2 for the respective primary end points, as described below for episodic patients, were nonsignificant, but the results were significant for PREVA (**Table 2**).[1,6,7] For all 3 trials, the mean age of patients was between 42 and 49 years, mostly male (at least 67%), who reported, at baseline, the average duration of attack to be between 60 and 105 minutes. In all trials, a significant proportion of patients were on standard treatments including triptans, high-flow oxygen, and prophylactic therapy, including verapamil and corticosteroids.

The ACT1 study sample was composed of two-thirds of patients with eCH and one-third of patients with chronic CH.[7] In a prespecified secondary endpoint, the efficacy for patients with eCH in ACT1 receiving gammaCore, the treatment resulted in a response rate (RR) more than 3 times higher compared with sham (RR, 3.2; 95% CI, 1.6-8.2; $P = .014$), a rate of being pain-free for >50% of attacks that was more than 2 times higher versus sham (RR, 2.3; 95% CI, 1.1-5.2; $P = .045$), and a difference of more than 30 minutes in duration of attacks, with a mean difference (MD) of –14.4 minutes for gammaCore compared with + 16.3 minutes for sham ($P < .01$). RR was defined as the proportion of all subjects who achieved a pain intensity score of 0 or 1 on a 5-point scale (0, no pain; 4, very severe pain) at 15 minutes after treatment initiation and who did not require rescue

TABLE 2. Summary of Study Outcomes in Subgroup Analysis of Patients With Episodic Cluster Headache in ACT1 and ACT2 and for Patients With Chronic Cluster Headache in PREVA Study[1,6,7]

Study, author, year	Treatment	Outcome 1		Outcome 2		Outcome 3	
		Response rate (RR) (%)[b,c]	RR (95% CI); *P*	Pain-free for >50% of attacks (%)	RR (95% CI); *P*	Change in attack duration in minutes (SD)	Difference; *P*
ACT1, Silberstein SD et al, 2016[a]	gammaCore (n = 73)	13/38 (34.2)	3.2 (1.6-8.2); .014	13/38 (34.2)	2.3 (1.1-5.2); .045	−14.4 (59.5)	−30.7; <.01
	Sham (n = 77)	5/47 (10.6)		5/47 (14.9)		16.3 (51.5)	
		Achieving pain-free attacks at 15 minutes (%)[c]	OR (95% CI); *P*	Change in pain intensity at 15 minutes (SD)	Difference; *P*	Response at 15 min for ≥50% of treated attacks[c]	RR (95% CI); *P*
ACT2, FDA-Label, 2017[a]	gammaCore (n = 50)	48/101 (47.5)	9.84 (2.2-44.1); <.01	−1.7 (0.4)	−1.1; .01	9/14 (64.3)	2.8 (1.0-8.1); .06
	Sham (n = 52)	5/81 (6.2)		−0.6 (0.2)		3/13 (23.1)	
		Pain-free in first attack at 15 minutes (%)[c]	OR (95% CI); *P*	Pain-free in all attacks at 15 minutes (%)[c]	OR (95% CI); *P*	Response at 15 min for ≥50% of treated attacks%[c]	RR (95% CI); *P*
Pooled ACT1 and ACT2, AAN, 2017[a]	gammaCore (n = 50)	38.5	--	24.1	--	42.3	--
	Sham (n = 52)	11.7		7.3		15.0	
		Change in attacks/week	Difference; *P*	Response in >50% of attacks (%)	Difference; *P*		
PREVA, Gaul C et al, 2016	gammaCore + SOC (n = 48)	−5.9	−3.9; .02	40.0	31.7; <.001		
	SOC only (n = 49)	−2.1		8.3			

AAN indicates American Academy of Neurology; OR, odds ratio; SD, standard deviation; SOC, standard of care.
[a]Data shown for patients with episodic cluster headache.
[b]Defined as the proportion of all subjects who achieved a pain intensity score of 0 or 1 on a 5-point scale (0, no pain; 4, very severe pain) at 15 minutes after treatment initiation.
[c]Did not require rescue medication use.

medication.[7] The safety profile for gammaCore was similar to sham. All device-related adverse events (AEs) reported were mild and transient with no serious device-related AEs reported. The number of patients (of all study participants) reporting at least 1 AE was 18 (25%) in the gammaCore group compared with 30 (40%) in the sham group. The number of patients reporting at least 1 device-related AE was 11 (15%) in the gammaCore group compared with 24 (31%) in the sham group. One patient in the gammaCore group reported a serious AE not related to the device (deep vein thrombosis), whereas none were reported in the sham group.

The ACT2 data, which have been presented but not published, were based on a study sample of approximately 30% patients with eCH and 70% patients with chronic CH.[1,19] Regarding efficacy for patients with eCH in ACT2 receiving gammaCore, compared with sham, the treatment resulted in nearly 10 times higher odds of achieving pain-free attacks with no rescue medication use in 15 minutes (OR, 9.84; 95%; CI, 2.2-44.1; $P = .01$), reduction in the intensity of attacks within 15 minutes (MD, −1.1; $P < .01$), and a rate nearly 3 times higher of achieving responder status at 15 min for ≥50% of treated attacks (RR, 2.8; 95% CI, 1.0-8.1; $P = .058$). Response status was defined as the proportion of all subjects who reported mild or no pain at 15 minutes after treatment initiation, and intensity score was based on a 5-point scale (0, no pain; 4, very severe pain).[1] The safety profile for gammaCore was also

similar to sham in ACT2. All device-related AEs were mild and transient with no serious device-related AEs reported. The number of patients reporting at least 1 AE was 23 (46%) in the gammaCore group compared with 22 (42%) in the sham group; the AEs were mild and transient, including lip pull, skin irritation, and metallic taste at the time of application. The number of patients reporting at least 1 device-related AE was 13 (26%) in the gammaCore group compared with 13 (25%) in the sham group. One patient in the gammaCore group reported a serious AE (severe lower abdominal and lower back pain), as did 1 in the sham group (severe depression).

In the Prevention and Acute Treatment of Chronic Cluster Headache (PREVA) trial treatment with gammaCore plus SOC resulted in a significant reduction in number of attacks per week from baseline values: −5.9 in the gammaCore + SOC group and −2.1 in the SOC group (MD, −3.9; $P = .02$). Over 30% more patients had a successful response in more than 50% of their attacks (gammaCore + SOC, 18 of 45 patients [40%], vs SOC alone, 4 of 48 patients [8.3%]; $P < .001$).[6] In addition, the patients on gammaCore + SOC experienced improvement in the EQ-5D health index (rising from 0.5 to 0.6) compared with no change in the patients who used the SOC alone during the randomization phase.[6] The safety profile for gammaCore + SOC was similar to that of SOC alone. AEs, particularly device-related, were all mild and transient with no serious device-related AEs reported. The number of patients reporting at least 1 AE was 25 (52%) in the gammaCore + SOC group compared with 24 (49%) in the SOC-alone group. The number of patients reporting at least 1 device-related AE was 13 (27%) in the gammaCore + SOC group compared with 7 (14%) in the SOC-alone group. Two patients in the gammaCore + SOC group reported a serious AE not device related (1 cholecystitis, 1 hematoma after scheduled surgery), whereas 2 were reported in the SOC-alone group (1 genital herpes simplex virus infection, 1 exacerbation of CH).

Observational/Open-Label Phase Studies on Impact of gammaCore

In the unblinded extension phase of the PREVA study, Gaul et al (2017) concluded that the prophylactic use of gammaCore led to rapid and sustained reductions in chronic CH attack frequency. Attack frequency remained significantly lower in the gammaCore + SOC group through week 3 of the extension phase ($P < 02$).[14] In a UK cohort study of 19 patients (8 episodic and 11 chronic), Nesbitt et al (2015) reported that the evidence suggested that gammaCore may be practical and effective as both an acute and a preventive treatment in patients with chronic CH. Further evaluation of this treatment using randomized sham-controlled trials was warranted at the time.[17] Marin et al (2016) reported in a retrospective analysis of 30 patients with CH (1 episodic and 29 chronic) that the use of gammaCore for acute treatment for 52 weeks resulted in significant reduction in CH attacks, duration of attacks, severity of attacks, and use of acute abortive medications.[20]

Cost-Effectiveness Studies

In a cost-effectiveness analysis reported by Morris et al (2016) based on a subset of PREVA study data from Germany, gammaCore + SOC was cost saving compared with SOC alone, from the German payer perspective.[16] In another cost-effectiveness analysis based on a subset of PREVA study data from the United Kingdom, Jenks et al (2016) found the incremental cost-effectiveness ratio (ICER) from the UK payer perspective was £13,368 per quality-adjusted life-year gained when comparing gammaCore + SOC with SOC alone.[21] The UK ICER threshold is £20,000.

Burden of Illness

Polson et al (2017) conducted and reported a cost analysis based on medical and pharmacy claims data from 4 regional health plans to evaluate differences in healthcare utilization and cost in 4174 patients with CH diagnoses (chronic, episodic, or "not defined") compared with a 1:1 control group of patients without headache-related conditions. The overall medical costs per patient for chronic (n = 724), episodic (n = 751), and nondefined (n = 2699) patients with CH were $30,502; $22,607; and $25,436, respectively, compared with $10,140 for nonheadache controls ($P < .01$). The overall prescription fills per patient for chronic, episodic, and patients with nondefined CH were 30.66, 23.90, and 24.79, respectively, compared with 12.34 for controls ($P < .01$). The corresponding overall pharmacy costs per patient for chronic, episodic, and patients with nondefined CH were $12,534; $8209; and $8570, respectively, compared with $4368 for controls ($P < .01$).[4] Limitations include use of claims data and that the sample may include migraine patients. Evidence from primary studies is summarized in **Table 3.**[4,14,16,17,20,21]

Summary of Evidence Presented in Recent Reviews

A pooled ACT1 and ACT2 analysis was also conducted and presented.[22] For patients with eCH, the pooled proportions of patients who responded (mild or pain free) to the first attack were 38.5% versus 11.7% ($P < .01$) for patients receiving gammaCore versus sham, respectively. The percentage of all treated attacks in the pooled analysis that were pain free at 15 minutes were 24.1% versus 7.3% ($P < .01$) for patients receiving gammaCore versus sham, respectively; and the pooled proportions of patients who responded (mild or pain-free) to >50% of their attacks were 42.3% versus 15.0% ($P < .01$) for patients receiving gammaCore versus sham, respectively.

Tepper et al (2013) reviewed the options, including gammaCore, for patients with medically refractory CH. At the time of the review, they concluded, "Because this device [gammaCore] does not require implantation, randomized controlled trials are clearly indicated."[8] Successful randomized trials have since been conducted.[1,6,7]

Ben-Menachem et al (2015) reviewed evidence regarding invasive versus non-invasive VNS for treatment of patients with CH. They found that the less frequent stimulation schedules used with

TABLE 3. Summary of Evidence From Primary Studies (non-RCTs or extension phases of RCTs)[4,14,16,17,20,21]

Study, author, year	Country	Study design	Sample size (n)	Age in years, mean (SD)	% Males	Population (episodic/ chronic)	Findings summary
PREVA, Gaul C et al, 2016	Multicenter	Post-randomization extension	97	43.7 (11)	69	Chronic CH	Prophylactic use of gammaCore led to rapid and sustained reductions in chronic CH attack frequency within 2 weeks after its addition to SOC and was associated with higher response rates than SOC alone.
Nesbitt AD et al, 2015	UK	Cohort study	19	47.5 (median)	57	CH (43/57)	These data suggest that gammaCore may be practical and effective as an acute and preventive treatment in chronic CH. Further evaluation of this treatment using randomized sham-controlled trials is thus warranted.
Marin J et al, 2016	UK	Retrospective analysis	30	47.9	37	CH (3/97)	Use of gammaCore resulted in significant reduction in CH attacks, duration of attacks, severity of attacks, and use of acute abortive medications.
PREVA, Morris J et al, 2016	Germany	Cost-effectiveness	--	--	--	Chronic CH	GammaCore + SOC was cost saving compared with SOC alone from the payer perspective.
Jenks MJ, 2016	UK	Cost-effectiveness	233	52 (12)	27.5	Chronic CH	Incremental cost-effectiveness ratio was £13,368 per QALY gained when comparing gammaCore + SOC versus SOC alone. The net monetary benefit was £631 and the net health benefit of 0.03 QALYs gained based upon a £20,000 per QALY threshold, driven by improvement in utility score with gammaCore.
Polson M et al, 2017	US	Cost analysis	4174 vs controls (non-CH)	52	48	CH: 751 episodic; 742 chronic; 2699 not defined	Costs per patient for patients with CH were $25,805 vs $10,140 for controls, and pharmacy costs per patient were $9197 vs $4368 for controls.

CH indicates cluster headache; QALY, quality-adjusted life-year; RCT, randomized controlled trial; SD, standard deviation; SOC, standard of care; UK, United Kingdom; US, United States..

nVNS may reduce the overall incidence of stimulation-associated AEs. Without a requirement for an expensive and potentially risky surgical procedure, nVNS may facilitate the earlier use of therapeutic VNS without the prerequisite of achieving a "treatment-refractory" status in the condition of interest.[23]

Holle-Lee et al (2016) reviewed clinical evidence regarding the management of patients with CH. They concluded that the advantages of nVNS lie in the safety of the technique and the low rate of associated AEs and that nVNS might be used not only as add-on prophylaxis in refractory chronic CH but also for episodic subtypes.[18]

Farmer et al (2016) reviewed evidence regarding VNS in clinical practice for patients with CH. They found that the vagus nerve continues to be an area of pathophysiological interest across a number of clinical disciplines. By extension, VNS, they concluded, had generated great interest and continued to be actively investigated. They noted that VNS is a potential treatment option that needs to be investigated, although its absolute place in clinical practice remains to be fully determined.[12]

Discussion

To summarize the findings of this review, the results from 2 double-blind, sham-controlled, randomized trials (ACT1, ACT2, and pooled analysis) demonstrated the superiority of gammaCore when added to other treatments (SOC) for episodic CHs by significantly reducing CH attack intensity, duration, and adjunct medication use. These trial findings and evidence that gammaCore does stimulate the vagus nerve contributed to the basis for the FDA clearance in April 2017 of gammaCore for treatment of pain associated with episodic

CH in the United States. This clearance was granted within the context of the FDA approval process for devices and how it differs from that for pharmaceutical products.[1,7]

In addition, the results of PREVA, an open-label, randomized trial, indicated significant reductions in both the frequency and duration of attacks in patients with chronic CH.[6,14] The result of these trials (ACT1, ACT2, and PREVA) also demonstrated the safety of gammaCore. Data from PREVA indicated that gammaCore use was cost-effective in patients with chronic CH, from the United Kingdom and German healthcare systems' perspectives.[16,21] Observational study results showed that patients with primary headaches, specifically those with CHs, often have multiple comorbidities and that these patients have significantly higher healthcare utilization and cost burden compared with patients with no reported comorbidities (eg, the average nonheadache patient).[4,5] gammaCore treatment for primary headache was associated with reductions in general practitioner appointments, referrals made by general practitioners, and with improvement in quality of life.[18]

It is important to step back and examine what these various pieces of evidence could mean for management of pain associated with eCH. All 3 trials were designed with gammaCore being adjunct to SOC, as it would be unethical to withhold SOC. Control patients received currently available treatments for the respective CH subtype. Therefore, it should be noted that the superiority of gammaCore is over and above the current SOC. Furthermore, regarding safety, it is remarkable that gammaCore not only has a safety profile similar to that of SOC, but as an added advantage, reduces the overall need for SOC medications. These trials were conducted in patients taking a range of medications and high-flow oxygen, and yet the impact of gammaCore corresponded to significant benefits. For example, in ACT1, gammaCore patients were 3 times more likely to respond, more than twice likely to achieve 50% pain-free status, and had their duration of attacks reduced by 30 minutes. Clinical symptom decreases of similarly substantial magnitude were also seen in ACT2. The observed AEs were mild and transient, while medication use and cost burden were reduced. These findings demonstrate robust efficacy and safety in a proportion of patients, both of which present a compelling argument for the advantages of gammaCore on efficacy and safety. These advantages need to be considered for the adoption of gammaCore in practice and for subsequent coverage by payers.

To further confirm gammaCore's contributions to the acute relief of symptoms in patients with eCH, additional evidence points to potential associated longer-term benefits, ones lasting for up to a year.[17] Granted, these retrospective studies do not have experimental designs. However, it is evident, based on real-world data, that a significant proportion of patients with CH[4] (or patients with primary headache[5]) have multiple comorbidities, with economic burdens significantly higher than those of patients without comorbidities or of the average nonheadache patients covered by payers. Furthermore, treatment of these patients with gammaCore is associated with reduction in healthcare utilization and improved quality of life.[18] By deduction, it is conceivable that broad adoption and coverage of gammaCore for treatment of patients with eCH will be beneficial to patients and payers.

Findings from the PREVA study demonstrated the sustained effectiveness of gammaCore in patients with chronic CH with robust results, as well.[6,14] In addition, the results of 2 cost-effectiveness studies, in the United Kingdom and in Germany, were persuasive: one showed dominance over SOC alone and the other with an ICER threshold of less than £20,000.[16,21] Findings from the ACT1 and ACT2 chronic patients' strata were not significant.

The implications of these findings, in addition to the clearance for eCH by the FDA in the United States, include gammaCore receiving regulatory approval in Australia, Brazil, Canada, Colombia, India, Malaysia, New Zealand, the European Union, and South Africa for the acute and/or prophylactic treatment of CH and migraine. In Europe, gammaCore is used for multiple indications; in the United Kingdom, this includes the prevention and acute treatment of migraine and CH, and gammaCore is used in the National Health Service.[9,10] In the European Union, gammaCore is a class IIa medical device; it has been granted Conformité Européenne marks for use in primary headaches, bronchoconstriction, epilepsy, gastric motility disorders, and depression and anxiety.[9]

The scientific and physiological bases for how and why gammaCore works as a nVNS are beginning to be better understood. While the exact mode of action has not been pinpointed, there is indeed evidence that gammaCore stimulates the vagus nerve[18] and that once the vagus nerve is stimulated, there are physiological consequences, some of which support the reduction in symptoms in CHs, migraines, and inflammatory disorders.[18,24] There is evidence of the effect of vagal stimulation on the cortex associated with treatment of epilepsy,[13,26-30] of reduction in pain in CH and migraine,[31] of reduction of inflammation, and of positive effects on psychiatric disorders.[11,32-34] A broader and more detailed review of the evidence around VNS and its mode of action is the subject of another review.[35] The broader use of gammaCore for multiple other indications in numerous markets, regulated independently and covered for reimbursement, along with the supporting evidence of the hypothesized modes of action, further support the observations of gammaCore's effectiveness: that it provides actual symptom relief and may have some longer-term benefits.

Based on these findings and considerations, the next logical questions are: does gammaCore add value to patients? And if so, does the value extend to payers? We examined these questions, with the focus on eCHs, in the context of current policies on reimbursement for VNS by payers in the United States. Based on findings of this review, we conclude that the use of gammaCore is beneficial to

patients with eCH, safely improving their outcomes and quality of life. Simultaneously, gammaCore reduces adjunct medication use, which also translates to value for payers and should impact current reimbursement policies.

First, gammaCore is an easy, practical approach to treatment of CH. It is simple enough for patients to apply, without assistance, during an attack. The device is safe, and the delivery of treatment doses is measured; doses cannot be wasted. Also, patients have indicated a preference for using gammaCore.[1] The treatment notably improves patient symptoms and results in a large reduction in the use of adjunct abortive CH medications, as well as overall utilization for comorbidities. When patients responded to gammaCore, the need for rescue medication was eliminated altogether. Therefore, for payers, gammaCore use may be associated with substantial long-term savings in patient costs.

Furthermore, gammaCore use is delivered via an electronic device, meaning that treatment delivery, adherence, and performance are relatively easier to monitor, particularly regarding treatment success, patient retention, utilization, and overall costs. This is particularly true when considering the growing trends toward performance-based coverage and that future generations of gammaCore devices will be Bluetooth-enabled and will seamlessly communicate with other devices, such as phones or laptops, for data capture.

Why is all this important to elucidate? For this reason: the current reimbursement policies for payers in the United States on VNS coverage explicitly state that primary headaches are not covered.[36-39] These policies predate gammaCore and are based instead on the expensive, surgically implanted, permanent invasive vagus nerve stimulation (iVNS) device that was approved specifically for treatment of refractory seizures. The iVNS costs approximately $30,000 to be surgically inserted. At the time these policies were written, it was reasonable, in the absence of trial-based evidence of the effect of VNS on primary headaches, to exclude primary headaches from coverage for iVNS. However, with the advent of 1) significantly less expensive nVNS and 2) new evidence from the ACT trials, the need to modify the policies, both in language used and in actual coverage, is warranted. First, the current policies refer to "VNS" and do not distinguish between iVNS (requires expensive device implantation) and nVNS (practical, handheld device, simple to use, inexpensive, safe). This poses a challenge as most payers use automated coverage adjudication algorithms. New policies should explicitly separate these 2 very different modes of treatment for very different indications. Second, the new evidence on gammaCore, approved for eCH by the FDA in April 2017 and used in Europe for primary headache prevention and treatment of acute attacks since 2013, should drive payer policies to adapt and cover gammaCore for eCH.

One other advantage to consider is that results of multiple studies indicate that patients with primary headache, including those with CH, should not, particularly from the payers' perspective, be viewed as single-morbidity patients. Instead, they should be considered as patients who commonly have multiple comorbidities; in comparison with average patients, patients with primary headache can cost payers up to 10 times more. Therefore, managing these patients adequately could not only markedly improve their health outcomes and quality of life, but also significantly reduce overall costs.

Limitations

This review, like any other, has strengths and limitations. One strength is that most evidence included in the literature review is peer-reviewed research, unless the research was very recently presented in conference proceedings and not yet published in the peer-reviewed literature. To support the legitimacy of the new evidence presented in this review, the data supporting the evidence are findings from robust, high-quality research designs. The efficacy of gammaCore in the secondary outcomes for eCH was demonstrated in double-blind, sham-controlled, randomized trials. The outcomes of the trials were clinically relevant and appropriately measured to support the hypothesis that gammaCore is superior to sham for patients with eCH.

One limitation associated with reviews is that the information available from publications that contribute to a review is as reported. This review, however, adds new information to the body of evidence, particularly in comparison with previous reviews. While authors of previous reviews had identified gammaCore as a beneficial intervention for patients with CH, they also pointed to a gap and a need for clinical trials to provide further evidence on its efficacy and safety. This review brings together the needed evidence to reduce the previously identified evidence gap.

The recommended future path for the various stakeholders—patients, researchers, electroCore, payers—is to collect real-world data that are specific to patients suffering from eCH and CH with regard to use or no use of gammaCore via a registry to monitor usage and performance measurement. Additionally, stakeholders should periodically review data from claims databases to evaluate long-term outcomes related to symptoms, utilization, cost, and reimbursement burden and the impact on comorbidities and all-cause healthcare utilization, to better understand the value associated with gammaCore use beyond symptom relief. With respect to evidence on patients with eCH, cost-effectiveness analysis using data from ACT1 and ACT2 have been published.[40] Also needed are continued research efforts, using randomized controlled trials, to characterize the benefits of gammaCore in other indications, including migraine, specific inflammatory illnesses, cardiac diseases, and psychiatric disorders, to mention a few.

Conclusions

gammaCore, cleared in April 2017 by the FDA, is supported by a physiological basis for the observed effects and provides value to

patients who suffer from eCHs. gammaCore would also provide value to payers, and there is sufficient evidence to support the need to modify current reimbursement policies, to differentiate nVNS from invasive iVNS, and to explicitly include coverage for gammaCore (nVNS) for eCH. ■

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