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Patient Experience With Non-Invasive Vagus Nerve Stimulator: gammaCore Patient Registry

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Mkaya Mwamburi, MD, PhD, MA
Eric J. Liebler

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The Role of Non-Invasive Vagus Nerve Stimulation in the Migraine Treatment Spectrum
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gammaCore is cleared by the FDA for acute and preventive treatment of cluster headache and the acute treatment of migraine in adults. Previously, only 2 treatments were approved for acute treatment of cluster headache while none were approved for preventive treatment. Following the initial FDA clearance, based on the ACT-1 and ACT-2 studies, a gammaCore Patient Registry (GPR) was designed to provide insights on the use of gammaCore and prescription patterns in the real-world setting and to characterize respective benefits and challenges during the acute treatment of episodic cluster headache. GPR was a prospective observational registry in which patients with episodic cluster headache (3rd edition of the International Classification of Headache Disorders criteria) who were prescribed gammaCore were invited to voluntarily enroll and provide information on their experiences between July 2017 and June 2018. Participants provided baseline information and were trained to self-administer treatment with gammaCore for cluster pain. Participants were also requested to record information for each cluster attack. Of the 182 patients who provided baseline demographic and cluster headache characteristics, 152 provided health index baseline data using EuroQol Health Index tool 5-level format (EQ5D-5L) and 17 patients provided attack data on a total of 192 cluster

headache attacks. The mean age was 49 years; 65% were male and 82% were white; the mean number of months of known diagnosis of cluster headache was 57; the mean number of attacks per cluster headache 4-week period was 14; and the mean pain score was 3.7 (0-4 scale) with a mean attack duration of 74 minutes. Sixty-seven percent of patients had used preventive treatments and 83% had used abortive treatments for cluster headaches; 25% of participants reported at least 1 comorbidity. The mean EQ5D-5L score (scale 0-1) was 0.83. Of the 192 cluster headache attacks reported, gammaCore was used in 116 (60%) attacks. Within this group, the mean pain score at the start of the attacks was 2.7, the mean number of stimulations used was 3.6, and the pain score after 30 minutes was 1.3. At 30 minutes, the pain of 81 (70%) attacks was reduced to none (27%) or mild (43%) (a pain score of 0 or 1) and in 94 (81%) attacks, patients experienced a reduction of at least 1 point in the pain score. This real-world observational evidence suggests that gammaCore adds clinically meaningful value to patients with episodic cluster headache by providing rapid pain relief and confirms that there is significant interest among prescribers in providing this new treatment and technology. This evidence further supports the need to redefine gammaCore as no longer investigational or experimental during considerations for reimbursement.

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Introduction

Cluster headache attacks affect between 0.1% and 0.3% of the US population.[1] They are debilitating, extremely painful, and can last up to 3 hours.[2] A non-invasive vagus nerve stimulator, gammaCore, has been cleared by the FDA for the acute and preventive treatment of cluster headache and acute treatment of migraine.[3-5] Prior to gammaCore's FDA clearance, the only FDA-approved therapies for the acute treatment of cluster headache attacks were injectable sumatriptan and ergotamine tartrate, and no treatments had been approved for prevention. The FDA clearance of gammaCore for the treatment and prevention of cluster headache was based on findings from 3 phase 3 trials: the ACT-1 and ACT-2 (Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache) and PREVA (Non-Invasive Vagus Nerve Stimulation for PREVention and Acute Treatment of Chronic Cluster Headache) studies, and a real-world evidence study.

gammaCore is not associated with any drug interactions and can be used several times within a 24-hour period with no multidose-related adverse effects (AEs). In the randomized, double-blind, sham-controlled ACT-1 and ACT-2 trials, gammaCore was superior to sham in rapidly aborting acute pain associated with episodic cluster headache and was well tolerated.[6] In PREVA, a prospective, multicenter, open-label, randomized controlled trial, gammaCore was also superior in reducing the number of attacks compared with controls in addition to being safe and well tolerated.[7,8]

GammaCore is a hand-held, battery-powered, non-invasive vagus nerve stimulator that has been reported to be safe; no patient has experienced cardiac or respiratory AEs in clinical trials.[6-10] In contrast, injectable sumatriptan and ergotamine tartrate, the currently approved pharmacological acute treatments for cluster headache, have significant practical and safety limitations including debilitating AEs, a variety of contraindications, and several notable drug interactions. Sumatriptan is a selective serotonin receptor agonist used as a subcutaneous injection to treat cluster headaches. Side effects include onset of non-migraine headaches, pain or chest tightness, flushing, pressure or heavy feeling parts of the body, feeling of weakness, feeling hot or cold, dizziness, drowsiness, nausea, and vomiting. Drug interactions of sumatriptan include ergot-containing medications (dihydroergotamine and ergotamine), sibutramine, monoamine oxidase inhibitors (isocarboxazid), selective serotonin reuptake inhibitors (fluoxetine and sertraline, serotonin), and norepinephrine reuptake inhibitors (venlafaxine and duloxetine).[11]

Following FDA approval of gammaCore in April 2017 and its subsequent launch in the United States, the gammaCore Patient Registry (GPR) was designed to provide a platform for patients receiving therapy to voluntarily provide information that could help provide a deeper understanding of gammaCore usage and improve patient care.[3] GPR was designed to provide real-world insight on prescription patterns and effectiveness of gammaCore and to characterize the respective benefits and challenges, thus providing policy makers with relevant evidence regarding the viability and practical use of gammaCore in the real-world setting.

Methods

GPR was a prospective observational program designed to enable patients with episodic cluster headache who were prescribed gammaCore to voluntarily enroll and submit information on their experiences between July 2017 and June 2018. Patients with established episodic cluster headaches, based on International Classification of Headache Disorders, 3rd edition, (ICHD-3) criteria, and who were prescribed gammaCore were requested to participate in GPR by their prescriber. ICHD-3 designation 3.1.1 for episodic cluster headache description is "Cluster headache attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 1 month." The diagnostic criteria are:

- Attacks fulfilling criteria for 3.1 Cluster headache and occurring in bouts (cluster periods)
- At least 2 cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of 1 month or more.

The patients received information during the enrollment visit on how to use gammaCore, how to log in to the patient portal, and how to complete baseline information and the attack tracker online. Participants were given standard training for self-administration of treatment with gammaCore, based on the on-label regimen used in ACT-2, with three 120-second stimulations consecutively administered at the onset of pain. If the pain was not aborted within 9 minutes after the beginning of the initial stimulation, the participants were able to treat themselves again with 3 additional consecutive 120-second stimulations. If an attack was not aborted by gammaCore, the subject had the option to use other treatments as rescue medications. Participants were requested to record information for each cluster attack using a web-based standardized questionnaire. Participants were asked to provide self-reported baseline information, including age, sex, race, and zip code; cluster attack history characteristics, such as duration of cluster attacks, frequency of cluster attacks per day, average duration of cluster headache cycles, severity, duration, and frequency of attacks over the preceding 4 weeks or in the last cluster attack cycle; any history of comorbidities and current medication used for acute and preventive treatment of cluster headache; quality-of-life assessment using EuroQol Health Index tool, 5-level format (EQ5D-5L); and whether they used technology, such as

mobile apps or web tools, for recording cluster data to complement cluster headache care. Pain was assessed on the cluster pain scale (0-4).

Results

Of the 182 participants who provided baseline data, 152 participants provided complete EQ5D-5L baseline data, and 17 provided documentation of a total of 192 cluster headache attacks. Among the 182 participants, 65% were men, 82% were white, and the mean age was approximately 49 years. The median household income of the zip codes where the participants lived was $66,000. The proportion of participants who had heard of gammaCore prior to GPR was 27%, while 75% of patients documented having received training for the use of gammaCore. The mean number of months of known diagnosis of cluster headache was 57. The mean number of patients reporting attacks in their respective previous cluster headache cycle was 14 per month with the mean pain score of 3.67 (0-4 scale), while the mean duration of attacks was 74 minutes.

Sixty-seven percent of patients reported using treatments to prevent cluster attacks, including 69 (44%) who were on verapamil, 32 (21%) on steroids, and 24 (15%) who had used nerve blocks. Eighty-three percent of patients were on treatments to abort acute pain associated with cluster headaches, including 89 (57%) participants who were on triptans, 65 (42%) on high-flow oxygen, and 11 (7%) on opioids. Thirty-nine (25%) patients had at least 1 comorbidity, including gastrointestinal symptoms, anxiety, depression, and sleep disorders; and 60 patients (39%) used mobile apps or web tools to help monitor their cluster attacks to complement their cluster headache care. The mean EQ5D score was 0.83. These findings are highlighted in **Table 1**.

Attack Details

Of the 192 attacks reported by 17 patients, gammaCore was used in 116 (60%). In these 17 patients, the mean pain score on a 0-4 scale at the start of the attack was 2.7, the mean number of stimulations used was 3.6, and the score after 30 minutes was 1.3 (mean reduction in pain score from baseline of 1.4) Eighty-one (70%) of the participants who

treated their attacks had no pain (31%) or mild pain (50%) at 30 minutes (27% with a score 0, and 43% with a score of 1). In 94 (81%) treated attacks, patients experienced a reduction in the pain score of at least 1 point. These findings are shown in detail in **Table 2**.

Discussion

The GPR tracked patients who were prescribed gammaCore for episodic cluster headache and participated voluntarily in the registry.[3] These results offer a real-world perspective on the use of gammaCore in the treatment of episodic cluster headache that aligns with findings from the ACT-1 and ACT-2 clinical trials and the growing body of evidence of gammaCore effectiveness.[6,8,10,12-15] This is the first real-world documentation of gammaCore use in the United States, which complements existing real-world data from the United Kingdom.[16] The patient characteristics in the GPR were similar to the characteristics of those enrolled in the ACT-1 and ACT-2 gammaCore trials.[6,8,10] The registry sample was predominantly male and white with an average age of approximately 49 years. From the patient-reported documentation, it was found that most attacks responded rapidly and with a clinically meaningful effect. Most attacks resulted in improved pain levels, with 27% of participants experiencing no pain and 43% experiencing mild pain within 30 minutes of the attack. These real-world observations, when compared with the clinical trial setting, align well with the expected efficacy and safety of gammaCore in the acute treatment of episodic cluster headache attacks. For the debilitating pain experienced by cluster headache patients, the observed level of pain relief within 30 minutes is clinically meaningful. In the pooled analysis of ACT-1 and ACT-2, the proportion of patients who were pain-free (pain score 0) to the first attack was 38.5% versus 11.7% (P <.01) for patients receiving gammaCore versus sham, respectively. The proportion of patients who responded to >50% of attacks was 64.5% versus 15.0% (P <.01) for patients receiving gammaCore versus sham, respectively.

Another important observation from the GPR was the reduction in average duration of attacks from 74 minutes reported at baseline to 47 minutes using gammaCore. This observed improvement from baseline was achieved with patients using an overall average

of 3.6 stimulations. This indicates that pain relief was achieved with a single gammaCore dose without a need for additional stimulations. These findings are significant, given that 83% of patients were on treatments prescribed to abort attacks, and 75% were treatments and procedures prescribed to prevent attacks. These findings affirm that gammaCore provides safe and effective pain relief to patients in the real-world setting and should therefore be considered for reimbursement by payers in the United States.[8,13,17,18] Treatment was safe with a straightforward dosage delivery and no reported AEs.

One limitation of the study was the relatively few patients who reported details on individual attacks. We believe this is because the number of attacks in this population who engaged in GPR was low during the time of participation. While it is possible that attack reporting may have been low if response to pain was poor, we believe that patients would have been equally inclined to report poor efficacy of a new product. However, for those who did provide attack details, GPR was able to provide insights on their respective experiences using gammaCore. The registry also demonstrated the interest and implementation of gammaCore by prescribers. The peak number of prescriptions and unique prescribers per week were 350 and 900, respectively, during the course of GPR enrollment. Training for doctors was straightforward and there were both initial prescriptions and refills, meaning patients found the need to continue treatment. Prescriptions were also written widely across 49 of the 50 states, and were evenly distributed geographically. Use of gammaCore is expected to increase based on its 3 FDA-approved indications, which include the prevention of cluster headache, the acute treatment of episodic cluster, and the acute treatment of migraine.[3-5,7,16,19-22]

Conclusions

This real-world observational study suggests that the FDA-approved gammaCore significantly adds a valuable therapeutic option for patients who suffer from episodic attacks of cluster headaches, based on patient-documented attacks. These data also confirm the significant interest among prescribers to provide the technology to patients who have few FDA-approved options for acute treatment and none for prophylaxis. The successful use of gammaCore in the real-world setting provides evidence to support the

need to redefine gammaCore as no longer investigational or experimental treatment, as well as for consideration for reimbursement by policy makers. In addition, evidence shows gammaCore is more cost-effective than the treatments that were standard of care (including sumatriptan and oxygen) prior to gammaCore introduction.***Author Affiliations:*** electroCore, Inc, Basking Ridge, NJ (EJL, PSS); profecyINTEL, LLC, Bridgewater, NJ (MM).

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Author Disclosures: Mr Liebler reports to having employment with electroCore, Inc. Dr Mwamburi reports to serving on an advisory board, receiving a receipt for payment, preparing a manuscript, owning stock, and having employment with profecyINTEL, LLC. Dr Mwamburi also reports to owning stock with Pharmacy Nexus 2017. Dr Staats reports to having board membership with World Institute of Pain (WIP) and serving on an advisory board for Medtronic, Abbott Laboratories, Nalu, and SPA Theraputic. He also reports to having employment with National Spine and Pain Centers and electroCore, Inc. Dr Staats has stock ownership with electroCore, Inc., and reports a possible conflict of interest with electroCore, Inc., as it is a manufacturer of gammaCore, a therapy used in headaches.

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Address correspondence to: mkaya.mwamburi@profecyintel.com.

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