

# The Emerging Role of gammaCore® in the Management of Cluster Headache: Expert Panel Recommendations

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**A** panel of 9 experts, including neurologists, other headache specialists, and medical and pharmacy directors, from 4 health plans (1 integrated delivery network and 3 plans with commercial, Medicare, and Medicaid lines of business), convened to discuss cluster headache (CH). Topics covered included the current treatment landscape, treatment challenges, economic impact of disease, and gaps in care for patients with CH. One major challenge in the management of CH is that it is underrecognized and frequently misdiagnosed, leading to delays in and suboptimal treatment for patients who suffer from this painful and disabling condition. The management of CH is challenging due to the lack of a robust evidence base for preventive treatment, the adverse events (AEs) associated with conventional preventive treatments, the variability of response to acute treatments, and the challenging reimbursement landscape for well-accepted treatments (eg, oxygen). The lack of effective prevention for many patients may lead to the excessive use of acute therapies, often multiple times each day, which drives the cost of illness up significantly.

The goal of the panel discussion was to discuss the role of gammaCore, the recently released first non-invasive vagus nerve stimulation (nVNS) therapy in the acute treatment of patients with episodic CH (eCH), in the management of CH. The panel reviewed current practices and formulated recommendations on incorporating a newly released therapy into CH management. The panel explored the role of traditional management strategies as well as that of gammaCore in the acute treatment of patients with eCH. Resources that may be useful in the treatment of patients with CH were also discussed.

## Clinical Background and Socioeconomic and Humanistic Burden of CH

CH is a neurological disorder characterized by frequent short-duration and severe attacks of head and orbital pain, with accompanying motor agitation and cranial autonomic signs and symptoms. Attacks usually begin between the ages of 20 and 40 years, but may start earlier or later.<sup>1</sup> CH can be subclassified into eCH and chronic CH

(cCH).<sup>2,3</sup> In eCH, patients experience at least 2 cluster periods of 7 days to 1 year in duration, which are separated by a headache-free interval of at least 1 month.<sup>2</sup> Attacks typically occur over a period of 4 to 12 weeks (ie, cluster periods). cCH differs from eCH in that patients experience daily or near-daily headaches, often multiple times per day, for more than 1 year without remission, or experience a headache-free interval of less than 1 month.<sup>2</sup>

Characteristic signs and symptoms of CH include, but are not limited to, sudden-onset excruciating pain in a periorbital or temporal location lasting between 15 and 180 minutes associated with agitation and autonomic signs, such as ipsilateral lacrimation, rhinorrhea, nasal congestion, facial flushing or pallor, ptosis, and/or miosis.<sup>2,3</sup> The affected side of the head typically does not change between attacks during a cycle or period. Headache specialist panel participants noted that CH attacks follow circadian rhythms and onset often occurs after a patient falls asleep. Attempts to mitigate attacks by changing sleep patterns generally are unsuccessful for these patients. Panel participants noted that patients usually have 1 to 3 attacks most days of the week during the cluster period; they cannot lie still, rock back and forth, and are quite irritable and agitated until the attack subsides.

The pathophysiology of CH is not entirely known; however, data suggest that there is trigeminal, hypothalamic, and brainstem involvement. Brain imaging revealed that the disorder involves abnormal activation patterns of the ipsilateral posterior hypothalamus and an autosomal dominant or autosomal recessive pattern of inheritance may be involved in some patients.<sup>2,4</sup> The estimated prevalence of CH in the United States ranges from 0.1% to 0.4%, with approximately 80% of patients affected by eCH and 20% of patients affected by cCH.<sup>5,6</sup> Patients with eCH may evolve to cCH and cCH may revert to eCH; between 4% and 13% of patients with eCH will evolve to cCH.<sup>2,7</sup> CH affects males 4.3 times more often than females; eCH affects males 2 to 9 times more often than females.<sup>1,5,8</sup>

CH is one of the most painful conditions an individual may experience, and it impacts patients' ability to perform daily activities, with 80% of patients reporting restricted daily activities as a result.<sup>9-11</sup>

In addition, CH is associated with a large socioeconomic burden for affected patients, but there is a lack of published literature surrounding the economic consequences of CH, and due to its low prevalence, the actual magnitude of its burden is unknown.<sup>9,10,12</sup> CH is sometimes referred to as “suicide headache” because of the elevated risk for suicidality among patients with the condition.<sup>13</sup> Research found that nearly 20% of patients with CH reported loss of employment and approximately 8% are unemployed or receiving disability services due to the disorder.<sup>13,14</sup>

### Gaps in Care and Current Approaches to Diagnosis and Treatment

A diagnosis of CH is based on a careful patient history, with further evaluation and workup, including general physical and neurological examination and, when indicated, imaging tests to exclude secondary causes. Because CH is a primary headache disorder, conventional diagnostics may be of little use; however, neuroimaging is mandatory when indicated because CH is rare and secondary causes are always a concern.<sup>2,6,9,13,15</sup> Diagnostic criteria for CH are published by the International Headache Society in the third edition of the *International Classification of Headache Disorders (ICHD-3)*, which is in beta version and, when finalized, is intended to be synchronized with the upcoming 11th edition of the World Health Organization's *International Classification of Diseases*.<sup>1</sup> In *ICHD-3* beta, the diagnostic criteria for CH require at least 5 attacks, each lasting 15 to 180 minutes, with a frequency between 1 every other day and up to 8 per day for more than half of the time when the disorder is active and with attacks accompanied by at least 1 of the following symptoms or signs, ipsilateral to the headache<sup>1</sup>:

- Conjunctival injection and/or lacrimation
- Eyelid edema
- Forehead and facial flushing and/or facial sweating
- Miosis and/or ptosis
- Nasal congestion and/or rhinorrhea
- Sensation of fullness in the ear
- A sense of restlessness or agitation

CH is underrecognized and frequently misdiagnosed.<sup>13</sup> Only 21% of patients receive a correct diagnosis upon initial presentation, and the average diagnostic delay for patients with CH is 5 years or longer, with an average of 3 healthcare providers seen before a patient receives a correct diagnosis.<sup>13,14,16</sup> The expert panel stated that the underdiagnosis of CH may be a result of the limited number of headache specialists in the United States and/or the lack of knowledge/recognition of the specific symptoms associated with the disorder by general neurologists and primary care providers. In the United States, there are just over 500 headache specialists who are currently board-certified.<sup>17,18</sup> Headache specialists include physicians who are board-certified through the United Council for

Neurologic Subspecialties (UCNS). There is also a Certificate of Added Qualification in Headache Medicine (CAQ) for physicians, physician assistants, advanced practice nurses, dentists, and psychologists.<sup>17</sup> As of September 2017, there are approximately 523 physicians nationwide with UCNS board-certification in headache medicine and fewer than 50 providers who have CAQ designation.<sup>17,18</sup>

Although there is a low prevalence of CH in the United States compared with migraine, the number of patients with CH far surpasses the number of available headache specialists, leaving many patients to seek care from their primary care provider, a provider in the emergency department setting, a provider who is not board-certified in headache medicine, or a neurologist without headache board-certification, certificate, or CAQ designation. If the patient does not have access to a provider, he or she may attempt to manage the condition with self-care, which is usually inadequate.<sup>17,18</sup> The headache specialist panel participants noted that patients often seek help from dentists, ophthalmologists, or ear, nose, and throat specialists due to the location of the pain in trigeminal nerve divisions V1 and V2 and the autonomic symptoms. Headache specialists are able to distinguish the unique presentation of CH from other headache disorders; however, providers who are not trained in this specialty may not be able to definitively diagnose CH if the patient presents with overlapping or similar features of other headache disorders.<sup>10</sup> In these instances, the presenting signs and symptoms may be mistaken for migraine, paroxysmal hemicrania, short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing, tension headache, so-called sinus headaches, or trigeminal neuralgia.<sup>10,19</sup> In addition, a variety of secondary causes, including vascular dissection and intracranial tumors/lesions, may mimic the symptoms and signs of CH, and appropriate investigations may be necessary to distinguish primary CH from secondary causes. The underrecognition, diagnostic delays, limited number of available specialists, and high suicide and disability rates highlight the need for improved identification of patients with CH.

Once a diagnosis is made, evidence-based treatment guidelines based on the literature for the management of CH are available from the American Headache Society (AHS) to help guide treatment.<sup>20</sup> The AHS guideline provides recommendations for the treatment of CH according to the American Academy of Neurology grades for treatment evidence present in the 2010 systematic review.<sup>20</sup> The **Table** provides descriptions of levels of recommendations.

For the acute treatment of CH, there is a level A recommendation for subcutaneous sumatriptan, zolmitriptan nasal spray, and high-flow oxygen (12-15 L/minute) administered only through a nonbreather face mask over the nose and mouth.<sup>20</sup> Parenteral dihydroergotamine (DHE) and subcutaneous sumatriptan both have FDA-approved indications for the acute treatment of CH. For transitional, short-term, or bridge prevention, there is a level A recommendation for suboccipital steroid injections, but the most

**TABLE.** AAN Grades for Treatment Evidence<sup>20</sup>

Level of Recommendation	Description
Level A	Treatment is established as effective for the given condition in the specified population; requires at least 2 consistent Class I studies
Level B	Treatment is probably effective; requires at least 1 Class I study or at least 2 consistent Class II studies
Level C	Treatment is possibly effective; requires at least 1 Class II study or 2 consistent Class III studies
Level U	Data for the treatment are inadequate or conflicting; treatment is unproven

AAN indicates American Academy of Neurology.

commonly used preventive treatment worldwide is verapamil, a calcium channel antagonist, which has a level C recommendation.<sup>20</sup> The AHS issued level B recommendations for the following treatments in the acute setting: sumatriptan nasal spray, oral zolmitriptan, and sphenopalatine ganglion stimulation, which is not approved for any indication in the United States at the current time, but is presently being evaluated in a randomized controlled trial.<sup>20</sup> Level B recommendations were also issued for civamide nasal spray in the prophylactic setting; however, work on its development stopped many years ago.<sup>20</sup>

While often effective, subcutaneous sumatriptan, zolmitriptan nasal spray, oxygen therapy, and suboccipital steroid injections have drawbacks and practical limitations. Subcutaneous sumatriptan and zolmitriptan nasal spray are expensive treatments with wholesale acquisition costs (WACs) exceeding \$60/dose.<sup>21</sup> AEs associated with subcutaneous sumatriptan include injection-site reactions, nausea, vomiting, dizziness, fatigue, paresthesias, and chest tightness.<sup>11,21</sup> A common AE of intranasal sumatriptan is a bad taste in the mouth.<sup>22</sup> Triptans are contraindicated in patients with ischemic, cardiac, cerebrovascular, or peripheral vascular disease, and the maximum FDA-approved doses of subcutaneous sumatriptan and intranasal zolmitriptan are 12 mg and 10 mg daily, respectively.<sup>23-25</sup> For patients who experience more than 2 attacks per day, particularly those who experience up to 8 attacks per day, the FDA-recommended maximum doses of these medications are insufficient to provide relief from their multiple attacks, and these patients will exceed the maximum daily doses of these treatments if they can access them because of the excruciating pain they experience.

Triptan overuse results in elevated treatment costs and medication waste.<sup>26</sup> One study revealed that nearly 70% of patients who experienced an average of 1 to 6 CH attacks per day were found to be using more than the recommended 12 mg of sumatriptan per 24-hour period, with some patients using as much as 36 mg during this time frame.<sup>27</sup>

Although advances have been made to increase portability, oxygen therapy is inconvenient for patients to transport and may pose a

fire hazard.<sup>13</sup> The AHS treatment guidelines recommend high-flow oxygen therapy at a rate of 12 to 15 liters per minute, and this results in the need for large oxygen tanks for this patient group. Patients must carry the oxygen tank with them to ensure the treatment is available at the time of an acute attack. As mentioned previously, CH attacks follow circadian rhythms and onset often occurs after a patient falls asleep. Home oxygen therapy may be beneficial for patients who experience nocturnal attacks.

The fire hazard risk is especially dangerous for patients who smoke, which is particularly problematic in this patient population, as Bahra et al in 2002 found that as many as 67% of patients with CH are known smokers.<sup>28</sup> During attacks, the restlessness experienced by patients may prevent them from keeping the nonbreather mask in place. Nonbreather masks also have portability issues, as these masks include a face mask as well as an attached oxygen reservoir bag and 1-way valve. Furthermore, many insurance companies restrict coverage of oxygen, as it is considered durable medical equipment, may only be a covered benefit for those with a respiratory diagnosis, and is not FDA-approved for the treatment of CH; this may present a barrier to accessing necessary treatment if patients are required to pay out-of-pocket to receive oxygen therapy.<sup>13</sup> At this time, neither Medicare nor Medicaid cover oxygen for CH.

The administration of suboccipital steroid injections is associated with minor AEs, including transient injection-site pain and, infrequently, hair loss at injection site and headache. Long-term use of steroids, regardless of route of administration, can result in Cushing's syndrome, blood glucose abnormalities, avascular necrosis of the femoral head, mood abnormalities, and other AEs.<sup>20</sup> This invasive procedure must be performed by a trained medical provider in an appropriate medical setting, which may be a less convenient and potentially costlier option than home-based treatments.

The AHS guidelines were published in 2016 and do not reflect the recent FDA clearance of the first nVNS therapy.<sup>29</sup> Therefore, these treatment guidelines will require updates to reflect the expansion of available CH treatments.

## The Role of gammaCore in the Management of CH

On April 18, 2017, the FDA cleared gammaCore, the first nVNS stimulation therapy for the acute treatment of pain associated with eCH in adult patients.<sup>29</sup> The hand-held medical device is applied at the neck and transmits electrical stimulation to the cervical branch of the vagus nerve through the skin.<sup>29</sup> Prior to the release of gammaCore, invasive stimulation of the vagus nerve had demonstrated efficacy in the treatment of refractory epilepsy, and the FDA granted LiaNova, formerly Cyberonics, approval for a surgically implanted VNS (iVNS) therapy.<sup>30</sup> iVNS devices were subsequently reported to have additional clinical benefits in reducing depression, thus resulting in FDA approval of these devices for the treatment of refractory depression.<sup>30</sup> In a report of patients who experienced intractable epilepsy and received VNS, 4 also suffered from episodic migraine, all of whom reported reduced frequency, average intensity, and maximum severity of their migraine attacks.<sup>31,32</sup>

Furthermore, in a case series of 6 patients who underwent VNS implantation for intractable primary headaches, 2 were diagnosed with cCH.<sup>31,33</sup> Both of the patients with cCH experienced improvements in their condition. One patient experienced marked improvements after 2 months, and the second patient responded to VNS as well.<sup>31,33</sup> These positive responses to treatment in conditions other than refractory epilepsy and depression highlighted the potential role of VNS therapy in primary headache disorders, including migraine and CH.<sup>31-33</sup>

Although the precise cause of CH is unknown, these headaches occur upon activation of the trigeminal-autonomic reflex pathway in the brainstem, and activation of the trigeminal nerve results in the ocular pain associated with CH as well as stimulation of the parasympathetic autonomic system, causing the associated symptoms of lacrimation, conjunctival injection, nasal congestion, and rhinorrhea.<sup>34</sup> In a preclinical animal model, nVNS suppressed acute nociceptive activation of trigeminocervical neurons, which is thought to be one of the mechanisms by which nVNS relieves the pain of eCH.<sup>3,15,35</sup>

GammaCore has regulatory approval for the acute and/or preventive treatment of CH, migraine, and medication overuse headache in the United Kingdom and European Union and in Canada for CH and treatment of migraine.<sup>36</sup> In the United States, gammaCore is approved only for the acute treatment of eCH. The safety and efficacy of gammaCore in the adjunctive preventive treatment of cCH was studied in the non-invasive vagus nerve stimulation for the PREvention and Acute Treatment of Chronic Cluster Headache (PREVA) trial, which is part of one of the largest clinical trial programs ever carried out in CH.<sup>37</sup> The PREVA trial was a prospective, open-label, randomized study that compared adjunctive preventive nVNS (N = 48) with standard of care (SOC) alone (ie, the control group) (N = 49). SOC preventive medications included, but were not limited to, verapamil, lithium, topiramate,

and corticosteroids.<sup>37</sup> The results of the study demonstrated that patients in the intent-to-treat population who received standard of care plus nVNS (N = 45) had a significantly greater reduction in the number of attacks per week compared with patients in the control group (N = 48) (-5.9 vs -2.1, respectively); (95% CI, 0.5-7.2;  $P = .02$ ).<sup>37</sup> In the standard of care plus nVNS group, 40% (18/45) of patients had response rates of 50% or greater for reductions in the number of attacks per week compared with 8.3% of patients (4/48) in the control group ( $P < .01$ ).<sup>37</sup> Additionally, treatment with nVNS was more effective the longer patients used the therapy.<sup>37,38</sup> Due to the lack of a control arm in this study, the FDA did not grant gammaCore approval for use in cCH prevention.

Patients in the nVNS treatment arm also demonstrated significant improvements in the quality-of-life measurement EQ-5D-3L VAS2 compared with baseline.<sup>37,38</sup> Furthermore, patients in the nVNS group in the randomized phase reduced their use of subcutaneous sumatriptan by 61% ( $P = .007$ ) and oxygen by 62% ( $P = .02$ ); patients in the control group did not experience a substantial reduction in acute medication use (10.2% increase and 14% decrease, respectively).<sup>37,38</sup> Upon study completion, 65% of patients stated that they would recommend nVNS to others and 75% of patients rated nVNS as easy to use.<sup>37,38</sup> The authors of the study concluded that adjunctive preventive nVNS is a safe and well-tolerated novel treatment for cCH that offers improved benefits compared with standard of care, with no serious device AEs.<sup>37</sup>

Compared with implantable VNS, occipital nerve stimulation, and sphenopalatine ganglion stimulation, gammaCore is a portable, easy-to-use device that can be self-administered by patients as needed to provide relief from eCH-related pain. In contrast, VNS is an invasive procedure requiring surgical implantation of electrodes around the cervical vagus nerve, electrodes which are then connected to a stimulating device that is implanted under the anterior chest wall.<sup>29,39-41</sup> Both iVNS and nVNS with gammaCore are safe and well tolerated; however, the implantable device and portable device differ in their AE profiles and treatment costs.<sup>39,40,42</sup> Implantable VNS has been associated with postoperative infections, and common AEs include transient cough, hoarseness, voice alteration, and paresthesias.<sup>42</sup> Potential AEs of gammaCore, all of which are transient, include hoarseness, shortness of breath, or voice alteration during treatment, and a tingling/pricking feeling where the device is applied.<sup>43</sup>

The FDA release of gammaCore was based on predefined subgroup analyses from 2 trials in the non-invasive vagus nerve stimulation for the ACute Treatment of Cluster Headache (ACT) clinical trial program, ACT1 and ACT2, which were designed to evaluate the safety and efficacy of gammaCore for the acute treatment of CH.<sup>29</sup> These trials were prospective, double-blind, placebo-controlled, randomized studies that evaluated the use of gammaCore versus a sham device.<sup>29,44</sup>

The primary efficacy end point for ACT1 was the percentage of patients who reported mild or no pain 15 minutes after treatment initiation with gammaCore for the first treated CH attack in the study.<sup>44</sup> In the total population, 26.7% of patients in the nVNS group had mild or no pain at 15 minutes after treatment initiation compared with 15.1% of patients in the sham group, but the results were not statistically significant ( $P = .1$ ).<sup>44</sup> The results of the ACT1 subgroup analysis, which evaluated 85 patients with eCH, demonstrated that 34.2% of patients in the active treatment group experienced a reduction in pain compared with 10.6% of patients who received sham treatment ( $P = .008$ ).<sup>29,45</sup> In the cCH cohort, however, patients did not achieve higher response rates in the nVNS treatment arm compared with the sham group (13.6% vs 23.1%, respectively;  $P = .48$ ).

The primary outcome for ACT2 was the percentage of total attacks that were pain free at 15 minutes after the onset of pain, with no use of rescue medication through the treatment period (30 minutes).<sup>44</sup> In the total population, 13.5% of patients in the nVNS group achieved pain-free status 15 minutes after the onset of pain compared with 11.5% in the sham group, but the results were not statistically significant ( $P = .713$ ).<sup>44</sup> The results of the ACT2 subgroup analysis, which evaluated 182 attacks in 27 patients with eCH, demonstrated that a significantly higher percentage of attacks were pain-free in eCH patients treated with gammaCore compared with placebo (47.5% vs 6.2%, respectively;  $P = .003$ ).<sup>29,44</sup> In the cCH cohort, however, patients did not perform better in the nVNS treatment arm compared with the sham group (4.8% vs 12.9%, respectively;  $P = .13$ ).<sup>44</sup>

Similar to the PREVA trial, treatment with gammaCore was found to be safe and well tolerated in both ACT1 and ACT2. The majority of AEs were considered mild and transient, and they occurred during active treatment.<sup>29,44</sup> AEs reported in ACT1 included application-site reactions (burning/tingling/soreness/stinging and skin irritation/redness/erythema), musculoskeletal disorders (lip or facial drooping/pulling/twitching), and nervous system disorders (dysgeusia/metallic taste).<sup>44</sup> In ACT2, 1 subject who received nVNS reported severe lower abdominal and lower back pain which was not considered related to treatment and resolved without intervention.<sup>44</sup> The results of ACT2 have been presented through oral and poster presentations and submitted to the FDA; the results also have been submitted for publication.

Both the ACT1 and ACT2 studies enrolled patients with eCH and cCH. No treatment difference was demonstrated between gammaCore and sham in the cCH cohorts in ACT1 or ACT2.<sup>37,45,46</sup> As mentioned above in the ACT1 trial, significantly higher sustained response rates with active versus sham treatment were observed in all subjects and the eCH cohort, but were not observed in the cCH cohort.<sup>45</sup> Authors of the study noted that the 15-minute time to first measurement of response, which was composed of an 8-minute nVNS stimulation period followed by a 7-minute period

of time, may not have been long enough to demonstrate treatment effects.<sup>45</sup> However, in the cCH cohort of the ACT2 study, a higher percentage of attacks achieving pain-free status at 15 minutes was not observed in the gammaCore arm compared with the sham arm (4.8% vs 12.9%, respectively).<sup>46</sup> The effectiveness of gammaCore has not been established in the acute treatment of cCH and the device is not approved in the United States for the preventive treatment of CH.<sup>44,46</sup> The answer to the question of why the nVNS device is effective in treating acute attacks in some patients with eCH, but is not effective in cCH, is not known and suggests the need for further research into the differences between eCH and cCH.

A late-breaking oral platform presentation at the 59th Annual Scientific Meeting of the AHS in Boston in June 2017 included the results of the pooled analysis of data from ACT1 and ACT2. This analysis evaluated the safety and efficacy of gammaCore as an acute treatment for eCH or cCH in more than 250 patients.<sup>47</sup> In ACT1 and the pooled analysis, significantly more patients with eCH achieved mild or no pain at 15 minutes after treatment initiation with gammaCore for the first treated cluster attack (ACT1 primary end point) compared with patients treated with the sham device (34% vs 11%;  $P = .01$ , and 39% vs 12%;  $P < .01$ , respectively), but not in ACT2 (50% vs 15%;  $P = .07$ ).<sup>47</sup> Additionally, a significantly greater proportion of all treated attacks achieved pain-free status at 15 minutes after treatment initiation (ACT2 primary end point) in eCH patients treated with gammaCore versus sham for ACT1 (15% vs 6%;  $P < .05$ ), ACT2 (35% vs 7%;  $P < .05$ ) and the pooled analysis (24% vs 7%;  $P < .01$ ).<sup>47</sup> No significant treatment differences were observed for either of these end points in the total CH population, the cCH population for ACT1, ACT2, or the pooled analysis.<sup>47</sup> No serious device AEs were reported.<sup>47</sup> Full results of the analysis will be available later this year.

Based on the safety and efficacy in some patients with eCH, the release of gammaCore represents a novel treatment that addresses a large unmet need in this patient population.<sup>6</sup> Treatment with gammaCore is not appropriate for all patient groups, and gammaCore is contraindicated in patients who have an active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device; those who have a diagnosis of carotid atherosclerosis; and in patients who have undergone cervical vagotomy.<sup>44</sup> Additionally, the safety and efficacy of gammaCore has not been evaluated in the following patients, and therefore is not indicated for: patients <18 years; pregnant women; patients with active cancer or cancer in remission; patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia; patients with an abnormal cervical anatomy; patients with a history of brain tumor; patients with aneurysms; patients who have experienced cerebral bleeding or head trauma; patients with a baseline history of cardiac disease or atherosclerotic cardiovascular disease, including congestive heart failure, known severe coronary artery disease or recent myocardial infarction (within 5 years); patients with a history of a prolonged

QT interval or arrhythmia; patients with a history of an abnormal baseline electrocardiogram; and patients with a history of seizures.<sup>44</sup>

### Panel Insights and Recommendations

The panel discussed the unmet needs of patients with CH by identifying the benefits and drawbacks of a variety of acute treatments, including subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen therapy, and provided additional insights based on issues observed among patients under their care.

The panel noted that the evidence and clinical experience that supports the use of high-flow 100% oxygen is significant and the tolerability of the treatment is excellent. Unfortunately, oxygen is often an impractical and nonportable treatment in the acute management of CH, for which treatment is needed immediately after CH attack onset, with the exception of patients who experience nocturnal attacks and who may benefit from home oxygen therapy. Additionally, as noted, the CMS published a policy regarding the use of oxygen for the treatment of CH among Medicare beneficiaries. This policy noted that there is currently insufficient evidence for home use of oxygen to treat CH, and home use of oxygen is only covered for beneficiaries with CH who are participating in an approved prospective clinical study comparing normobaric 100% oxygen with at least 1 clinically appropriate comparator for the treatment of CH.<sup>48</sup> At the time of CMS' publication, no clinical trials involving the home use of oxygen to treat CH had been approved by CMS for Coverage with Evidence Development, resulting in no access to oxygen therapy for the treatment of CH for Medicare and Medicaid beneficiaries.<sup>48</sup>

Although the AHS treatment guidelines note that there is insufficient evidence that DHE 1 mg nasal spray is effective in improving headache response, in a separate AHS publication, DHE 1 mg intramuscular injection was noted to be effective in the relief of acute attacks of CH, and it is FDA-approved for this purpose.<sup>20,49</sup> The panel commented that DHE injections are an effective and sometimes preferred therapy for some healthcare providers and patients; however, DHE injections are also costly, with a WAC of approximately \$125 per 1-mg injection.<sup>21</sup> The AHS treatment guidelines also include lithium and verapamil as preventive therapies, with a Level C recommendation of possibly effective for the treatment of CH.<sup>20</sup> The panel commented that verapamil and lithium have both been prescribed in practice, but both, particularly the latter, have tolerability and safety issues.

Following a review of the data supporting the release of gammaCore, the panel agreed that gammaCore is a safe, well-tolerated, and effective acute treatment option for patients with eCH; it represents a first-line acute treatment option for patients with eCH. The panel referenced supporting literature that highlights the behavioral health disorders associated with CH, including published reports suggesting that patients with CH demonstrate worse working memory, disturbance of mood, and poorer quality

of life compared with healthy controls.<sup>11</sup> CH is associated with an almost 3 times increased odds ratio of lifetime depression compared with controls, and patients with cCH have a higher prevalence of lifetime depression and sleep disturbance compared with patients with eCH.<sup>50</sup> Patients with cCH and eCH experience significant impairments in noneconomic and economic domains (eg, disability, working life, and psychiatric complaints). Psychiatric comorbidity (ie, depressive symptoms, signs of agoraphobia, and suicidal tendencies) is highest in cCH.<sup>51</sup> Headache specialist panel participants also reported high rates of opioid and other illicit substance misuse and abuse in patients with CH.

In addition to the comorbid behavioral health conditions associated with CH, the panel noted that there is a major socioeconomic impact on patients and society as a result of both direct and indirect costs caused by lost ability to work.<sup>12</sup> As previously mentioned, patients with eCH have extended periods of disability, whereas patients with cCH experience annual periods of remission totaling less than 1 month. The panel stated that the availability of nVNS with gammaCore may offer patients with eCH improved control of attacks, which in turn may result in improvements in quality of life, including the potential to return to work in an increased capacity. Treatment with gammaCore may also offer payers a potential cost savings opportunity if the use of gammaCore results in a reduction in use of rescue medications such as sumatriptan injections or oxygen therapy as demonstrated in the PREVA study.<sup>37</sup> All panel participants were in agreement that payers should offer coverage of gammaCore to plan members who have a diagnosis of eCH; these payers would then need to determine whether gammaCore coverage should be provided under the pharmacy or medical benefit.

### Future Implications and Considerations

In addition to insights regarding gaps in care and recommendations for payer coverage of gammaCore, the panel noted that additional studies need to be conducted in the United States to verify the role of gammaCore in the preventive therapy of eCH and cCH. Following the review of clinical trials and case series of gammaCore in the United Kingdom, the National Institute of Health and Care Excellence published guidance regarding the use of gammaCore for the prevention and acute treatment of CH and migraine; it noted that gammaCore is safe and can be used in the National Health Service (NHS).<sup>52</sup>

The use of gammaCore for the prevention and acute treatment of cCH was studied in the PREVA study, which demonstrated medication usage savings of approximately €1736 (\$1897 in USD) per patient per year and an average total cost savings of €2799 (\$3059 in USD) per patient per year.<sup>37,53</sup> Additional future studies conducted in the United States may be helpful in clarifying and identifying additional patient groups (ie, preventive treatment of CH) in which treatment with gammaCore may be beneficial.<sup>37,45,46</sup> The savings demonstrated in the model are based on the price

of €0.87/dose for nVNS in Germany.<sup>54</sup> Investigational treatments in clinical trials, including anti-calcitonin gene-related peptide monoclonal antibodies and sphenopalatine ganglion stimulation, are likely to be more expensive than gammaCore.

The panel also noted that there may be a potential role for gammaCore in the treatment of migraine, and it awaits the results of the ongoing PRESTO and PREMIUM clinical trials evaluating the safety and efficacy of gammaCore for the acute treatment of migraine attacks and the prevention of episodic migraine, respectively.<sup>54</sup> Data from these 2 studies are expected later this year.

## Conclusions

In conclusion, the panel agreed that the treatment guidelines should be updated to reflect the role of gammaCore as a first-line, acute treatment option for patients with eCH and that payers should offer coverage of gammaCore to their members who have a diagnosis of eCH. Coverage determinations will require decisions to permit coverage under the pharmacy or medical benefit, as well as updates to payers' pharmacy and/or medical policies to reflect coverage of this novel treatment. Healthcare providers, including headache specialists and neurologists, and payers are encouraged to remain up-to-date regarding the results of ongoing clinical trials evaluating the use of gammaCore for the acute and/or preventive treatment of migraine to ensure that patients are being appropriately treated for these conditions and that they have access to treatment through their insurers. ■

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