

Transcutaneous (Non-implantable) Vagus Nerve Stimulation (e.g. gammaCore-S®)

Policy MP-036

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.

Description:

The vagus nerve, a large nerve that runs down the neck, into the chest and down into the gut which connects the lower part of the brain to the heart, lungs and intestines. Vagus nerve stimulation (VNS) uses short bursts of electrical energy directed into the brain via the vagus nerve. Stimulating this nerve has been studied as a way to treat several different types of conditions such as; seizures that don't respond to medication, depression, headaches, epilepsy, tinnitus and pain.

Historically, stimulation of the vagus nerve is performed using a pulsed electrical stimulator implanted within the carotid artery sheath. There are also devices available that are implanted at different areas of the vagus nerve to treat conditions like obesity. More recently, non-implantable VNS devices (also referred to as n-VNS or transcutaneous VNS [t-VNS]) have been developed to treat migraine and cluster headaches. An example of this type of device is gammaCore-S® (ElectroCore™, LLC) which is a noninvasive handheld prescription device intended to deliver transcutaneous vagus nerve stimulation for the acute treatment of pain associated with episodic cluster headaches and migraines in adults.

GammaCore-S initially received 510(k) clearance for treatment of both acute migraine and episodic cluster headache with expansion of its FDA clearance to include cluster headache prevention. Therapy using the gammaCore device is self-administered, and for cluster headache prevention consists of two daily treatments, each of which is comprised of three consecutive two-minute stimulations. To do so, patients apply a conductive gel to the side of their neck, and then hold the gammaCore to the same area while it dispenses a mild electrical stimulation through the skin and to the vagus nerve. Acute migraine therapy involves 6 stimulations encompassing 3 two minutes stimulations the first two separated by 20 minutes and the second and third by 2 hours. For acute cluster headaches, the patient uses three 2 minute

stimulations separated by 3 minutes. For use in cluster headache prevention, the three 2 minute stimulations are administered twice a day.

The gammaCore-S device is not available for purchase. It is preloaded with a specific number of stimulations and requires a monthly “prescription”. If prescription not ‘refilled’ the device will automatically lock out and become nonfunctional.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans does NOT cover non-implantable (transcutaneous) vagus nerve stimulation devices (e.g. gammaCore-S®) as they are considered investigational for all indications.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at

<http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)

3. Medicare Plans

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at:

<http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)

Clinical Rationale

No systematic reviews have been published on noninvasive vagal nerve stimulation. A Hayes Search and Summary published on April 16, 2019 concluded current evidence demonstrates conflicting findings regarding the use of gammaCore-S® for the treatment of headaches (migraine and cluster).

In support of the Hayes findings, Nesbitt et al. (2015), in an open-label observational study of 19 patients (11 chronic, 8 episodic) described the initial experience with a noninvasive vagus nerve stimulator (nVNS), designed to provide portable, non-invasive, transcutaneous stimulation of the vagus nerve, both acutely and preventively, as a treatment for cluster headaches (CH). The authors concluded their findings suggested that nVNS may be practical and effective as an acute and preventive treatment in chronic cluster headaches. Yet, they acknowledge the size and design of their study did not allow for definitive conclusions related to efficacy and safety and, further evaluation of this treatment using randomized sham-controlled trials are needed.

Silberstein et al. evaluated non-invasive vagus nerve stimulation (nVNS) as an acute cluster headache (CH) treatment in a 2016 randomized, double-blind, sham-controlled (ACT1) study. They studied one hundred fifty patients aged 18 Years to 75 Years, randomized to receive either sham control or nVNS treatment for less than or equal to one month; completers could enter a 3-month nVNS open-label phase. The primary end point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. The authors concluded that nVNS provided significant, clinically meaningful, rapid, and sustained benefits for episodic cluster headache but not for chronic cluster headache, which affected results in the total population. However, in one of the largest randomized sham-controlled studies for acute CH treatment, the response rate was not significantly different (vs sham) for the total population.

In another 2016 open-label study of 56 patients, Grazzi et al. assessed noninvasive vagus nerve stimulation (nVNS) for the prophylactic treatment of menstrual migraine/menstrual related migraine (MM/MRM). There were no safety/tolerability concerns. Even though the findings suggested that nVNS may be an effective treatment to reduce the number of MM/MRM and analgesic use without safety or tolerability concerns in patients, the authors concluded that more RCTs are needed to validate these findings.

Yuan, et al. (2017) also noted neurostimulation to be an emerging area in headache treatment through invasive vagus nerve stimulation (VNS) and noninvasive vagus nerve stimulation (nVNS). When using VNS or nVNS, multiple brain areas can be modulated to alleviate pain, which reduces a pharmacological need. Early case series from epilepsy and depression cohorts using invasive VNS as well as nVNS showed a serendipitous reduction in headache frequency and/or severity. Long-term use of nVNS seemed to exert a prophylactic effect for both chronic migraine and chronic cluster headache while chronic VNS seems to be associated with a better outcome that improves over time. Progression in nVNS clinical efficacy over time suggests an underlying disease-modifying neuromodulation and appears to be as effective as the invasive counterpart for many indications. In conclusion, the authors found potential for both invasive VNS and nVNS in the management of distinct types of headache disorders. However, a clearly effective double-blinded, sham-controlled study that has a strongly positive primary endpoint for various types of headache is needed.

Furthermore, in studies focusing on acute migraine pain, Tassorelli et al. in 2018 assessed 248 patients using noninvasive vagus nerve stimulation (nVNS) for the treatment of migraines. The purpose of this multicenter, double-blind, sham-controlled trial was to determine the safety, efficacy, and tolerability of nVNS. Patients were randomized to receive nVNS or sham within 20 minutes of the onset of pain of episodic migraines with or without aura, then repeat treatment if the pain had not improved within 15 minutes. nVNS (n = 120) was superior to sham (n = 123) for pain freedom at 30 minutes (12.7% vs 4.2%) and 60 minutes (21.0% vs 10.0%) but not at 120 minutes (30.4% vs 19.7%) after the first treated attack. A post hoc repeated-measures test provided further insight into the therapeutic benefit of nVNS through 30, 60, and 120 minutes. nVNS demonstrated benefits across other endpoints including pain relief at 120 minutes and was safe and well tolerated. They concluded, the findings of this trial suggested effective pain relief, tolerability, and practicality of nVNS for the treatment of acute episodic migraines in as early as 30 minutes and up to 60 minutes after an attack. However, the role of nVNS in migraine therapy needs further exploration in long term follow-up with ongoing large-scale, randomized, sham-controlled trials.

In a 2018 double-blind cohort (ACT2) study, Goadsby et al. compared randomly assigned patients, with cluster headaches (CH) (episodic [eCH] or chronic [cCH]), for acute treatment with either non-invasive

vagus nerve stimulation (nVNS) or a sham device during a 2 week period. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status within 15 minutes after treatment initiation, without rescue treatment. The full analysis set comprised 48 nVNS-treated (14 eCH, 34 cCH) and 44 sham-treated (13 eCH, 31 cCH) subjects. For the primary endpoint, nVNS (14%) and sham (12%) treatments were not significantly different for the total cohort. In the eCH subgroup, nVNS (48%) was superior to sham (6%). No significant differences between nVNS (5%) and sham (13%) were seen in the cCH subgroup. After combining both eCH and cCH patients, the study found nVNS was no different to sham. The authors concluded that for the treatment of CH with nVNS was superior to sham therapy in eCH but not in cCH attacks. However, this study had limitations, such as its short duration, which did not allow for evaluation of continued/change in response with long-term nVNS therapy, the imbalance between CH subtypes, and the eCH subgroup comprised <30% of subjects by letting them alter their CH treatment regimens, which confounded the study results. It was felt these limitations made it impossible to discern if the changes in outcomes were attributable to nVNS therapy or other changes in treatment.

A 2019 systematic review (Reuter et.al.) assessed the available data of clinical trials to inform clinical decisions about non-invasive neuromodulation therapies for migraine and cluster headache as a practical and safe alternative to pharmacologics. Comparisons of these therapies are difficult because of the heterogeneity in study designs. PubMed, Cochrane Library and ClinicalTrials.gov databases and the WHO's International Clinical Trials Registry Platform were searched for relevant clinical studies of non-invasive neuromodulation devices for migraine and cluster headache, 71 were identified between the timeframe of January 1st, 1990 to January 31st, 2018. Study designs compared recommendations of the International Headache Society for pharmacological clinical trials, the only available guidelines for migraine and cluster headache. Non-invasive vagus nerve stimulation (nVNS), single-transcranial magnetic stimulation and external trigeminal nerve stimulation (all with regulatory clearance) were well studied compared with the other devices, for which studies frequently lacked proper blinding, sham controls and sufficient population sizes. The authors concluded that nVNS studies demonstrated the most consistent adherence to available guidelines and studies of all neuromodulation devices should strive to achieve the same high level of scientific rigor to allow for proper comparison across devices. Hopefully, device-specific guidelines for migraine and cluster headache will soon be available, until then adherence to current guidelines for pharmacological trials will remain a key consideration for investigators and clinicians.

Another 2019 review (Cvetkovic et.al.) analyzed available evidence regarding efficacy and safety of different neurostimulation modalities for the treatment of chronic migraine and cluster headaches in a small subsets of patients who failed to respond to pharmacological treatment and may benefit from alternative treatment methods. In the last decade, neurostimulation is being explored as a potential treatment option for the patients with chronic, severely disabling refractory primary headaches. To alleviate pain, specific nerves and brain areas have been stimulated, and various methods have been explored: deep brain stimulation, occipital nerve stimulation, and sphenopalatine ganglion stimulation are among the more invasive ones, whereas transcranial magnetic stimulation and supraorbital nerve stimulation are noninvasive. Vagal nerve stimulation can be invasive or noninvasive, though this review included only data for noninvasive VNS. In conclusion, although neurostimulation treatments have demonstrated good efficacy in many studies, it still has not been established as a standard treatment in refractory patients.

Hoffman et.al (2019) also reviewed neuromodulation techniques and how they are playing an increasing role in the treatment of primary headaches. While initially reserved for refractory cases they are now

increasingly taken into consideration in earlier treatment phases and in non-refractory situations. One of the main reasons for this paradigm shift is that most neuromodulation techniques are better tolerated as compared to the majority of pharmacological approaches. However, non-invasive vagal nerve stimulation, sphenopalatine ganglion stimulation, external trigeminal nerve stimulation, occipital nerve stimulation as well as single-pulse and repetitive-pulse transcranial magnetic stimulation have their limitations that should be considered. Such as the invasive techniques require a surgical intervention with all the potential complications that may arise. The authors found that most of the evidence is based on open-label studies. Sham devices used in controlled studies remain problematic as they either do not produce the paresthesias perceived during stimulation or induce some degree of stimulation. Therefore, some of the techniques provide an effective expansion of available treatment options but their indications should be thoroughly evaluated before treatment is considered.

Lastly, a 2019 UpToDate review on "Cluster headache: Treatment and prognosis" concluded that "When chronic cluster headache is unresponsive to medical treatments, various surgical interventions and neurostimulation techniques are potential treatment options, though none are clearly established as effective. In such cases, it is particularly important to exclude potential causes of secondary cluster headache. Neurostimulation techniques, including sphenopalatine ganglion stimulation and vagus nerve stimulation, appear promising but remain investigational. Destructive surgical procedures are unproven and should be viewed with great caution."

Applicable Coding

CPT Codes

No applicable codes

HCPCS Codes

E0770 Functional electrical stimulator, transcutaneous stimulation of nerve and/or muscle groups, any type, complete system, not otherwise specified

E1399 Durable medical equipment, miscellaneous

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