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Medical Policy

Subject:	Vagus Nerve Stimulation		
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Description/Scope

This document addresses the indications for use of an implantable vagus nerve stimulation (VNS) device, the electronic analysis of the implanted neurostimulator pulse generator system, and non-implantable (transcutaneous) VNS devices for the treatment of medically and surgically refractory seizures associated with intractable epilepsy and as a treatment of other conditions. Implantable devices may deliver stimulation in an open-loop fashion with continuous but intermittent ('ON' and 'OFF' cycles) stimulation of the vagus nerve (a hand-held magnet allows on-demand stimulation to interrupt seizure activity), or may utilize detection of extra-cerebral indicators, for example, cardiac-based seizure detection (also known as "responsive devices", "devices with an automatic stimulation mode", or "closed loop devices" that specifically use tachycardia as a surrogate marker for seizure prediction).

Note: The use of vagal nerve *blocking* for the treatment of morbid obesity is addressed in the following document:

- CG-SURG-83 Bariatric Surgery and Other Treatments for Clinically Severe Obesity

Position Statement

Medically Necessary:

A. Implantation of a vagus nerve stimulation device is considered **medically necessary** in an individual with medically and surgically refractory seizures as evidenced by:
   1. Failure of more than one trial of single or combination antiepileptic medications, as evidenced by persistent seizures or intolerable side effects of drug therapy; **and**
   2. Individual has failed or is not a candidate for resective epilepsy surgery.

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B. Electronic analysis of an implanted neurostimulator pulse generator system for vagus nerve stimulation is considered **medically necessary** when the implantation occurred because the above criteria were met.

C. Replacement or revision of an implanted neurostimulator pulse generator system (with or without lead changes) for vagus nerve stimulation is considered **medically necessary** when:
   1. The implantation occurred because the above criteria were met; **and**
   2. The current implanted device is no longer functioning appropriately.

Investigational and Not Medically Necessary:

A. Implantation of a vagus nerve stimulation device is considered **investigational and not medically necessary** when criteria are not met and for all other conditions, including, but not limited to:
   1. Alzheimer's disease; **or**
   2. Anxiety and mood disorders; **or**
   3. Asthma; **or**
   4. Autism; **or**
   5. Bipolar disorders; **or**
   6. Bulimia; **or**
   7. Cerebral palsy; **or**
   8. Crohn's disease; **or**
   9. Depression; **or**
   10. Essential tremors; **or**
   11. Headaches (including cluster and migraine headaches); **or**
   12. Heart failure; **or**
   13. Obesity, including obesity-related food cravings; **or**
   14. Pain syndromes (including fibromyalgia); **or**
   15. Seizures (that do not meet the above medically necessary criteria); **or**
   16. Sleep disorders.

B. Electronic analysis of an implanted neurostimulator pulse generator system for vagus nerve stimulation is considered **investigational and not medically necessary** when the medically necessary criteria for device implantation are not met.

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~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. . The member's contract benefits in effect on the date that services are rendered must be used. . Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. .Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

C. Replacement or revision of an implanted neurostimulator pulse generator system for vagus nerve stimulation (with or without lead changes) is considered **investigational and not medically necessary** when the medically necessary criteria for device implantation are not met or the current implanted device is functioning appropriately.

D. Non-implantable vagus nerve stimulation devices are considered **investigational and not medically necessary** for all conditions, including, but not limited to:
   1. Headaches, acute or preventive treatment (including cluster headaches [episodic or chronic], migraine headaches, and other headaches); **or**
   2. Pain syndromes; **or**
   3. Schizophrenia; **or**
   4. Tinnitus.

Rationale

Implantable VNS as Treatment of Medically and Surgically Refractory Seizures

In 1997, the U.S. Food and Drug Administration (FDA) approved a VNS device called the NeuroCybernetic Prosthesis (NCP®) system (Cyberonics, Inc. [now LivaNova USA, Inc., Houston, TX) through the premarket approval (PMA) process. The device was approved for use in conjunction with drugs or surgery "…as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures." The company currently markets the system as VNS Therapy®. ~~In April 1999, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination (NCD 160.18) for implantable VNS as an effective treatment for medically refractory partial onset seizures when surgery is not recommended or has failed.~~

In 2015, the FDA approved the AspireSR generator, the first VNS Therapy System that provides responsive stimulation when tachycardia is detected. The AspireSR includes an autostimulation mode that utilizes a customizable cardiac algorithm to detect relative heart rate increases to predict ictal onset and deliver automatic vagus nerve stimulation to prevent seizures before they occur or more quickly end them when they do occur (closed loop system). The FDA approved the most recent implantable VNS therapy system, the SenTiva in October 2017. Like the AspireSR, the SenTiva device includes an autostimulation mode. The Sentiva also includes additional features such as small size, data gathering and a tablet-based interface. In addition to the autostimulation mode,

both devices have a manual mode. Both devices are approved for use in individuals with drug-resistant epilepsy aged 4 years and older.

~~Published evidence from well-designed multimember trials with long-term follow-up demonstrates the use of VNS as an adjunct to optimal use of antiepileptic drugs in the treatment of medically refractory individuals with at least six partial onset seizures per month reduces seizure frequency by approximately 25% after 3 months of treatment (Morris, 1999; Murphy, 1999). In individuals who achieve an initial reduction in seizure frequency, the beneficial treatment effect appears to be maintained and may increase with time. Appropriate candidate selection for implantable VNS is based on the presence of seizures that are refractory to medical therapy, either in terms of persistence of seizures, or due to intolerable side effects of drug therapy, and not on the number of seizures alone (Fisher, 1999).~~

The long-term efficacy and safety of VNS therapy in children with medically refractory seizures, including those with Lennox-Gastaut Syndrome (LGS), has been reported in numerous retrospective case series, multicenter and observational studies, and randomized controlled trials (RCTs) (Alexopoulos, 2006; Benifla, 2006; De Herdt, 2007; Elliott, 2011c; Healy, 2013; Klinkenberg, 2012; Kostov, 2009; Orosz, 2014; Tecoma, 2006; You, 2007; You, 2008). Additional retrospective case series measuring the long-term effects of VNS for medically and surgically refractory seizures in adults and the pediatric population have been published in the peer-reviewed medical literature. Significant reductions in seizure frequency with possible cumulative effect are reported along with a reduction in surgical complications and untoward side effects with chronic VNS therapy (Coykendall, 2010; Elliott, 2011a; Elliott, 2011b; Ghaemi, 2010; Kabir, 2009; Morris, 1999; Murphy, 1999; Siddiqui, 2010; Vale, 2011; Yu, 2014). Englot and colleagues (2011) performed the first meta-analysis of VNS efficacy in epilepsy, identifying 74 clinical studies with 3321 participants with intractable epilepsy. These studies included three blinded, ~~randomized controlled trials~~RCTs (Class I evidence); two nonblinded, ~~randomized controlled trials~~RCTs (Class II evidence); ten prospective studies (Class III evidence); and numerous retrospective studies. After VNS implantation, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after greater than 1 year of therapy. At the last follow-up, seizures were reduced by 50% or more in approximately 50% of the individuals, and VNS predicted a ≥ 50% reduction in seizures (main effects, odds ratio of 1.83; 95% confidence interval [CI], 1.80-1.86). Individuals with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. The authors concluded that VNS is an effective and relatively safe adjunctive therapy in individuals with medically refractory epilepsy not amenable to resection. ~~However, i~~It is important to recognize that complete seizure freedom is rarely achieved using VNS and that approximately 25% of individuals do not receive any benefit from therapy. Ryvlin and colleagues (2014)

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published a ~~randomized controlled trial~~RCT reporting long-term quality of life outcomes for 112 individuals with drug-resistant focal seizures, which supports the beneficial effects of VNS for this group.

~~Orosz and colleagues (2014) conducted the largest retrospective multicenter study to date to gain insight into the long-term impact of VNS therapy in children with drug-resistant epilepsy. A total of 347 records of children, aged 6 months to 17.9 years (at the time of implant), were assessed for change in seizure frequency following VNS device implantation from baseline to 24 months of follow-up. At 6, 12, and 24 months after implantation, 32.5%, 37.6%, and 43.8% of children, respectively, had ≥ 50% reduction in baseline seizure frequency of the predominant seizure type. A subgroup of children who had no change in antiepileptic drugs during the study had a higher response rate. Favorable changes in secondary outcomes were reported in seizure duration, ictal severity, postictal severity, quality of life, clinical global impression of improvement, and safety measurements. A post hoc analysis demonstrated a statistically significant correlation between VNS total charge delivered per day and an increase in response rate. The study did not identify any new safety issues with use of VNS therapy in this group of children.~~

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In a Cochrane review, Panebianco and colleagues (2015) systematically reviewed the available evidence in the peer-reviewed medical literature for the efficacy and tolerability of VNS when used as an adjunctive treatment for individuals with drug-resistant partial epilepsy. In five trials which included 439 participants, VNS appeared to be effective and well tolerated for the treatment of partial seizures. Results of the overall efficacy analysis showed that VNS using a high stimulation paradigm was significantly better than low stimulation in reducing frequency of seizures. In addition, results for the outcome "withdrawal of allocated treatment" suggested that VNS was well tolerated as withdrawals were rare. The authors reported no significant difference was found in withdrawal rates between the high and low stimulation groups; however, limited information was available, so important differences between high and low stimulation could not be excluded. Adverse effects associated with implantation and stimulation included hoarseness, cough, dyspnea, pain, paresthesia, nausea and headache, with hoarseness and dyspnea more likely to occur on high stimulation than low stimulation. ~~The authors suggest, however, that further high-quality research is needed to fully evaluate the long-term efficacy and tolerability of VNS for drug resistant partial seizures.~~

In 2013, the American Academy of Neurology (AAN) (Morris, 2013) released an updated guideline evaluating the evidence regarding the efficacy and safety of VNS for epilepsy. The guideline states that VNS may be considered

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for seizures (both partial and generalized) in children, for LGS-associated seizures. VNS may also improve mood when used in the treatment of adults with epilepsy although this should be considered a secondary reason for VNS.

Harden and colleagues (2017) reported on the incidence rates and risk factors for sudden unexpected death in epilepsy (SUDEP) in different epilepsy populations in a 2017 practice guideline from the AAN and American Epilepsy Society. Considering a systematic review of the literature, the guideline states:

> The evidence is very low or conflicting that the following factors are associated with altering SUDEP risk:
> - Vagus nerve stimulator use for more than 2 years (however, current research does not rule out the possibility of a beneficial effect and, further, the potential effect of epilepsy surgery on reducing GTCS frequency and epilepsy severity on reducing the risk of SUDEP).

Closed Loop Systems

Tzadok and colleagues (2019) retrospectively analyzed the data from 46 individuals aged 5 through 31 who underwent AspireSR implantation. The group included new insertions (n=29) and VNS replacement with the AspireSR device (n=17). The primary objective, the response rate, was defined as the proportion of individuals with a 50% or greater seizure frequency reduction. At a mean follow-up time of 13 months, there was a 62% responder rate in those for whom AspireSR was the first VNS implantation, and a 59% responder rate in those who replaced a previously implanted VNS with AspireSR. A total of 5 individuals were seizure free; 4 of these were new insertions. The authors noted the responder rate of an open-loop VNS treatment varied by study from 43.8% to 55.6%, and that the differences in responder rates may be correlated to differences in follow-up periods as VNS response rates have been found to increase over time. The results suggest that the closed-loop device can provide a benefit to those in whom resective surgery is not a viable option.

A retrospective study collected data from individuals with an AspireSR device implanted by a single surgeon in order to determine efficacy of AspireSR in new implants and to compare the efficacy of AspireSR to preceding VNS models (Hamilton, 2018). Cases were divided into two cohorts, those with a new implant (n=51) and those who had been switched over from a previous model (n=62). Within each cohort, the seizure burden was compared between the periods before and after implantation. For those with new implants, the pre-VNS seizure burden was compared to the post-AspireSR burden. For those who previously had a VNS device, the pre-VNS, post-initial VNS and post-AspireSR burdens were compared,

with comparisons made between the first and second periods to assess the improvement resulting from the initial VNS placement, and between the second and third periods, to assess any additional improvement from the AspireSR device. The median follow-up duration was 19.9 months (0.5-37.5 months) in the new implantation cohort and 17.3 months (1-32 months) in the previous VNS device cohort. In the new implantation cohort, prior to insertion, the subjects reported a median 192 seizures/year. This decreased to a median of 64/year post insertion. More than half of the participants (59%) reported a 50% or greater reduction in seizure burden post-implantation, with 41% of these individuals reporting an 80% or greater reduction. The cohort included 16% classified as poor responders, who, at best, had their seizures dampened or aborted with swiping of the magnet, as well as 10% of these reported no antiepileptic benefit from VNS therapy. For individuals with a previous VNS device, there was a further significant reduction in seizure burden following placement of the AspireSR device from 90/year to 72/year, with 71% reporting a 50% or greater improvement over their initial VNS. Within this cohort, 31% of individuals reported a greater response to the AspireSR compared to their previous VNS device. The cohort also included 1 individual who reported a smaller benefit from AspireSR therapy compared to their initial VNS and 1 individual reported no antiepileptic benefit from either VNS therapy. The authors noted that following battery change to AspireSR "approximately one-third (29%) of patients will have < 50% benefit, one-third (35%) will have 50-79% benefit and another one-third (35%) will have even ≥ 80% benefit" while less than 2% of individuals did not report a benefit.

In a prospective, multicenter, industry-sponsored study, Boon and associates (2015) evaluated the performance and safety of a cardiac-based seizure detection algorithm in a closed loop system that automatically triggers VNS. The study objective was to demonstrate a seizure detection sensitivity of at least 80% for ictal tachycardia seizures by at least one detection threshold setting. A total of six seizure detection algorithms are available to be customized for individuals; participants were randomized to one of three different settings (≥ 20%, ≥ 40%, ≥ 60% above baseline heart rate). The associated false positive (FP) rate was also studied. Individuals with drug resistant epilepsy who were implanted with the AspireSR device (n=31) were continuously monitored by EEG and ECG at an epilepsy monitoring unit for 3-5 days. Data was available for 66 seizures in 16 individuals. A sensitivity of 80% or greater was achieved at multiple settings. False positive ranged from 0.5 to 7.2/hour. Individuals experienced statistically significant reduction in complex partial seizure severity compared to baseline. Seizure activity stopped during stimulation in 4/4 (100%) simple partial, 6/11 (54.5%) complex partial, and none of the secondarily generalized seizures (0/2). Long term, the responder rate was reported at 24.1% (7/29) at 3 months, 20.0% (6/30) at 6 months, and 29.6% (8/27) at 12 months. There were no unanticipated adverse device effects and surgical implantation was reported as well tolerated. The device demonstrated the ability to detect seizures based on cardiac changes at a threshold as low as 20% above baseline heart rate.

While ~~randomized clinical trials~~RCTs directly comparing conventional ("open loop") devices to devices with an automatic stimulation mode" ("closed loop") have not been conducted, available evidence suggests that both devices are likely to produce equivalent therapeutic results.

Implantable VNS as Treatment of Refractory Depression

In July 2005, Cyberonics, Inc. (now known as LivaNova USA, Inc, Houston, TX, USA) received FDA premarket approval for the VNS Therapy™ System "…for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments." The data presented to the FDA consisted of a case series of 60 individuals receiving VNS (Study D-01), a short-term (3-month) randomized sham-controlled clinical trial of 221 individuals (Study D-02), and an observational study comparing 205 individuals on VNS therapy to 124 individuals receiving ongoing treatment for depression (Study D-04) (George, 2005; Rush, 2000). Individuals who responded to sham treatment in the short-term ~~randomized, controlled trial~~RCT (approximately 10%) were excluded from the long-term observational study.

The primary efficacy outcome was the relief of depression symptoms, assessed by any one of many different depression symptom rating scales. A 50% reduction from baseline score was considered to be a reasonable measure of treatment response. In the studies evaluating VNS therapy, the four most common instruments used were the Hamilton Rating Scale for Depression (HAMD), Clinical Global Impression, Montgomery and Asberg Depression Rating Scale (MADRS), and the Inventory of Depressive Symptomatology Self-Related (IDS-SR). The case series data reported rates of improvement, as measured by a 50% improvement in depression score of 31% at 10 weeks to greater than 40% at 1 to 2 years. This appeared to stabilize out to 2 years, but there were substantial losses to follow-up (n=42 at 2 years versus~~.~~ original sample of 59) (Marangell, 2002; Rush, 2000; Sackeim, 2001). Natural history, placebo effects, and the expectations of the individual and their medical practitioner make it difficult to infer efficacy from this case series data.

The D-02 randomized trial (Rush, 2000; Rush, 2005a) compared VNS therapy to a sham control, (implanted but inactivated VNS), reporting a non-statistically significant result for the principal outcome at 3 months. A total of 15% of VNS subjects responded versus 10% of control subjects (p=0.31). The IDS-SR was considered a secondary outcome, showing a difference that was statistically significant in favor of VNS (17.4% versus~~.~~ 7.5%; p=0.04). All other outcomes assessed in the trial did not show statistically significant differences between groups.

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The observational study comparing subjects participating in the ~~randomized clinical trial~~RCT and a separately recruited control group (D-04 versus~~.~~ D-02) evaluated VNS therapy out to 1 year, showing a statistically significant difference in the rate of change of depression score ~~(p<0.001)~~ (George, 2005; Rush, 2000). This study was conceived after the results of the ~~randomized clinical trial~~RCT were known. The outcomes of this study, however, may have been confounded by issues such as unmeasured differences between subjects, nonconcurrent controls, differences in sites of care between subjects with VNS therapy and controls, and differences with regard to concomitant therapy changes. Analyses performed on subsets of subjects cared for in the same sites and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness of VNS with almost no statistically significant differences. Considering these concerns about the quality of the observational data, these results lack strong evidence to support the effectiveness of VNS therapy as a treatment for refractory depression.

Nahas and colleagues (2005) evaluated the safety and effectiveness of VNS in an acute phase pilot study of 59 individuals with treatment-resistant major depressive episode (MDE). They examined the effects of adjunctive VNS over 24 months in this adult population. Adults treated in the outpatient setting with chronic or recurrent major depressive disorder or bipolar (I or II) disorder and experiencing a treatment-resistant, non-psychotic MDE (DSM-IV criteria) received 2 years of VNS. Changes in psychotropic medications and VNS stimulus parameters were allowed only after the first 3 months. Response was defined as ≥ 50% reduction from the baseline 28-item ~~Hamilton Rating Scale for Depression (~~HAMD-28~~)~~ total score, and remission was defined as a HAMD-28 score ≤ 10. Based on last observation carried forward analyses, HAMD-28 response rates were 31% (18 of 59) after 3 months, 44% (26 of 59) after 1 year, and 42% (25 of 59) after 2 years of adjunctive VNS. Remission rates were 15% (9 of 59) at 3 months, 27% (16 of 59) at 1 year, and 22% (13 of 59) at 2 years. By 2 years, 2 participant deaths (unrelated to VNS) occurred, 4 participants withdrew from the study, and 81% (48 of 59) were still receiving VNS. Longer-term VNS was generally well tolerated; however, at 24 months the accumulated serious adverse events affected 42% of the participants. The investigators concluded that their findings suggest that individuals with chronic or recurrent, treatment-resistant MDE may show long-term benefit when treated with VNS. However, the number of responders and the degree of their improvement fluctuated over the 2-year study. Since there was no control group, it is difficult to determine if this was due to the VNS or the natural course of chronic depression. There was no information on whether any subjects failed to respond to either electroconvulsive therapy (ECT) or details about antidepressant augmentation strategies utilized prior to being accepted into this study.

An open-label, uncontrolled, unblinded study of VNS therapy, in addition to concomitant treatment with antidepressant medications (stable for 4 weeks prior to study entry, during the recovery period and the acute study phase), enrolled individuals with treatment-resistant depression (TRD) or bipolar I or II disorder at nine European

sites (D03) (Schlaepfer, 2008). ~~The study protocol was similar to the D01 study conducted in the United States, except that: (1) the study inclusion required a score ≥ 20 on the HAMD-24 scale in the D03 study, as opposed to ≥ 20 on the HAMD-28 scale in the D01 study, (2) the maximum age at entry was 80 in the D03 study and 70 in the D01 study, and (3) the number of failed adequate medication trials was greater than or equal to two medication trials but less than six medication trials in the D03 study versus greater than or equal to two medication trials in the D01 study. During the long-term follow-up period, adjustments in stimulation parameters and medications were permitted.~~ Of the 74 participants implanted with the device, 4 participants withdrew during the acute study period. A total of 7 participants dropped out during the first year long-term study period, 5 participants due to adverse events or lack of efficacy, and 2 participants committed suicide. ~~Primary outcomes were reported as a reduction in the severity of depression as measured by the HAMD-24, but HAMD-28 was assessed and used for comparison of results to the D01 study.~~ The baseline HAMD-28 score averaged 34. After 3 months of VNS, response rates (≥ 50% reduction in baseline scores) reached 37% and remission rates (HAMD-28 score < 10) 17%. Response rates increased to 53% after 1 year of VNS, and remission rates reached 33%. Response was defined as sustained if no relapse occurred during the first year of VNS after response onset; 44% of participants met these criteria. Median time to response was 9 months. Most frequent side-effects were voice alteration (63% at 3 months of stimulation) and coughing (23%). ~~Comparing results of this study to the D01 study results, t~~The investigators reported a decrease in severity of depression after 3, 6, 9, and 12 months compared to baseline HAMD-28 score~~, reaching significance in both samples over time, with higher efficacy in the D03 study compared to the D01 study~~. ~~This was attributed to the lower measures of baseline depression in the D01 study.~~ The investigators, however, reported "a major shortcoming" of this study ~~, as in the United States D01 study,~~ was that effectiveness was not assessed in a sham-controlled design, "limiting interpretations on clinical utility." ~~In addition, t~~The authors suggest in future trials of VNS for depression, "it might therefore be valuable to study the specific characteristics of personality of a patient population with treatment resistance interested in this procedure (VNS) to judge whether personality features contribute differentially to treatment effects" ~~(Schlaepfer, 2008)~~.

Bajbouj and colleagues (2010) reported 2-year follow-up data on individuals with TRD in a small open-label, longitudinal cohort study. The results indicated that 53.1% (26 of 49) of individuals met the treatment response criteria (≥ 50% reduction in the HAMD-28 scores from baseline) and 38.9% (19 of 49) fulfilled the remission criteria (HAMD-28 scores ≤ 10) while on VNS. These results are limited in demonstrating improved health outcomes due to the small study population and lack of a comparison group. Cristancho and colleagues (2011) followed participants with major depressive disorder (n=10) and with bipolar disorder (n=5) at 6 and 12 months post-VNS implantation. At the 12-month follow-up, 4 of 15 participants responded and 1 of 15 participants remitted according to the principal response criteria. These outcomes are comparable to those observed in previous VNS efficacy studies and with a similar side effect profile, however, the small sample size, lack of a comparison

group, and short-term outcome measurements limit this study in drawing conclusions concerning the net health benefit of VNS for this group of individuals.

In a multicenter double-blind study, Aaronson and colleagues (2013) compared the safety and effectiveness of different stimulation levels of VNS therapy as adjuvant treatment in 331 individuals with a history of chronic or recurrent bipolar disorder or a current episode of major depressive disorder. The intent of the trial was to show that "high" and "medium" electrical "doses" (charge) would produce superior clinical outcomes relative to a "low" electrical dose. Participants with a history of failure to respond to at least four adequate dose/duration antidepressant treatment trials from at least two different treatment categories were randomized to one of three dose groups. After 22 weeks, the current stimulation dose could be adjusted in any of the groups. At follow-up visits at weeks 10, 14, 18, and 22 after enrollment, there was no statistically significant difference between treatment groups in comparison of the primary outcome measure, a change in IDS-Clinician Administered (IDS-C) score from baseline. The mean IDS-C score improved significantly for each of the groups from baseline to 22-week follow-up. At 50 weeks of follow-up, the proportion of the small number of 22-week responders with a durable outcome was greater in the "high" and "medium" electrical "dose" groups than in the "low" dose group. Most participants completed the study; however, there was a high rate of reported adverse events, including voice alteration in 72.2%, dyspnea in 32.3%, and pain in 31.7%. Limitations of this study include the interpretation of improvement in IDS-C scores over time due to the lack of a controlled (no treatment) comparator group and, that approximately 20% of the participants had a history of bipolar disorder. Therefore, the results may not be representative of a homogeneous group of individuals with treatment-resistant unipolar depression.

Aaronson and colleagues (2017) evaluated long-term outcomes from the 5-year post-marketing surveillance study of individuals with TRD treated with VNS or "treatment as usual." This multicenter, prospective, open-label, non-randomized, longitudinal, observational registry study conducted at 61 United States sites included 795 individuals who experienced a major depressive episode (unipolar or bipolar depression) of at least 2 years duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Prior to enrollment, registry participants (except for those enrolled in the VNS dose-finding study, referred to as the D-21 study; NCT00305565) were allowed to select the treatment arm of their choice; however, some individuals were assigned by study site to receive the alternate treatment (n=301, number of participants in the treatment-as-usual arm). Participants in the VNS arm (n=494) underwent implantation surgery before visit 2 (baseline). Post-baseline follow-up visits for all participants were scheduled at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months. Data was collected on medical status, adjustment of mood disorder therapy, and concomitant treatments (with no restrictions). The primary efficacy measure was response rate, defined as a decrease of ≥ 50% in baseline MADRS score at any post-baseline visit during the 5-year study. Secondary efficacy

measures included remission. Safety analysis included participants in the treatment-as-usual arm who completed the visit 2 requirements and those in the VNS arm who had undergone device implantation before visit 2. At baseline, the mean MADRS score was 29.3 (standard deviation [SD] equals 6.9) for the treatment-as-usual group and 33.1 (SD equals 7.0) for the VNS arm. The registry results indicated that participants in the VNS arm had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-year cumulative response rate (67.6% compared with 40.9%, respectively; p<0.001) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%, respectively; p<0.001). A subanalysis demonstrated that among participants who had previously responded to ECT, those in the VNS arm had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%, respectively; p=0.006). For ECT nonresponders in the VNS arm, the response rate was 59.6% (95% CI, 50.2, 68.4), compared with 34.1% (95% CI, 21.8, 48.9) for ECT nonresponders in the treatment-as-usual arm (p<0.001), with statistically significant separation beginning after 2 years of treatment and continuing until completion of registry participation. Several limitations to this study exist, including those previously cited in the original study, and the long-term evaluation of data from a participant registry. The naturalistic, observational study design did not allow for random assignment of participants to treatment groups; thus, participants were not blinded to treatment. A significant number of participants in both groups withdrew early from the study. Of the 494 participants in the VNS arm, 461 (93%), 289 (59%), 313 (63%), 334 (68%), and 300 (61%), respectively, completed all 5 years of the registry (the variable numbers in the VNS arm are due to D-21 study participants who rolled over into the registry at various time points after implantation). Of the 301 participants in the treatment-as-usual arm, 224 (74%), 185 (62%), 168 (56%), 149 (50%), and 138 (46%), respectively, completed all 5 years of the registry. Of the 358 patients (45%) who withdrew early, 195 were from the VNS arm (40%) and 163 were from the treatment-as-usual arm (54%). The reasons for early withdrawal were similar between the treatment arms. Finally, the significantly higher treatment response rate observed in the VNS arm may represent a treatment effect, as participants with an implanted device may have had a higher expectation of therapeutic improvement; in addition, inclusion of D-21 study rollover participants in the VNS arm who may have previously experienced a positive response with VNS may have been more likely to participate in the registry.

~~*Other Considerations*~~

~~In April 1999, CMS determined that implantable VNS was not medically reasonable and necessary for TRD. On July 15, 2005, the FDA granted premarket approval to Cyberonics, Inc. for their VNS Therapy System for the adjunctive long-term treatment of chronic or recurrent depression for individuals 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more antidepressant treatments. CMS (2007) subsequently initiated a national coverage analysis (NCA) to reconsider resistant~~

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depression as an additional indication for implantable VNS. After a review of the evidence, CMS concluded in a national non-coverage determination (effective May 4, 2007) that VNS is not reasonable and necessary for individuals with TRD. On February 15, 2019, CMS posted a decision memorandum that covers implantable VNS for TRD when offered in a CMS-approved research study.

Comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy. Comparison of any of the potential interventions in the treatment of TRD, nonpharmacologic or otherwise, is hampered by variable definitions of TRD, heterogeneity of study participants, and lack of clinically meaningful interpretation of pertinent outcome measures as relevant studies did not assess both response and remission rates.

Summary

The available evidence in the peer-reviewed medical literature is insufficient to permit conclusions regarding the long-term effect of VNS therapy on improving health outcomes, or its effect compared with alternative therapies for TRD. Additional randomized controlled trialsRCTs are needed to address the complex and unresolved issues of dose, sham control, participant blinding, and length of treatment phase to demonstrate the efficacy of VNS for TRD.

Implantable VNS as Treatment of Other Conditions

Treatment of Chronic Heart Failure

De Ferrari and colleagues (2011) conducted an open-label, phase II trial of VNS therapy utilizing the CardioFit® device (BioControl Medical, Yehud, Israel - New Hope, Minnesota) in 32 individuals with New York Heart Association (NYHA) class II-IV chronic heart failure. Significant iImprovements were reported in measures of quality of life, 6-minute walk test, and left ventricular ejection fraction (from 22 ± 7 to 29 ± 8%; p=0.003). An international multicenter randomized clinical triaRCTl (INOVATE-HF) assessing the safety and efficacy of the CardioFit System in symptomatic individuals with heart failure is currently recruiting participants (Hauptman, 2012). To date, the CardioFit device has not received FDA clearance for VNS therapy or any other indication.

Zannad and colleagues (2014) reported results from a randomized, sham-controlled trial (NECTAR-HF) with outcomes from VNS in individuals with severe left ventricular (LV) dysfunction despite optimal medical interventions. A total of 96 participants implanted with VNS were randomized 2:1 to VNS ON or VNS OFF for 6 months. Programming of the generator was performed by a physician unblinded to treatment assignment, while all

other investigators and site study staff involved in endpoint data collection were blinded to randomization. A total of 59 of the 63 participants randomized to the intervention had paired pre-post data available; 28 of 32 participants randomized to control had paired data available. Analysis of trial data was a modified intention-to-treat. There were no significant differences between groups for the primary endpoint of change in left ventricular end systolic diameter (LVESD) from baseline to 6 months ~~(p=0.60 between-group difference in LVESD change)~~. Other secondary efficacy end points related to LV remodeling parameters, LV function, and circulating biomarkers of heart failure, did not differ between groups with the exception of a 36-Item Short-Form Health Survey Physical Component score, which showed greater improvement in the VNS ON group than in the control group (from 36.3 to 41.2 in the VNS ON group versus~~.~~ from 37.7 to 38.4 in the control group; p=0.02). A major limitation of this study includes flaws in the blinding of participants, which may have biased the subjective outcome data reporting.

Premchand and colleagues (2014) evaluated the use of a novel autonomic regulation therapy (ART) using either left or right VNS in 60 individuals with heart failure with reduced ejection fraction. In the ANTHEM-HF study, VNS was randomly assigned to right- or left-sided implantation (n=29 and 31, respectively). Participants followed from baseline to 6-month follow-up experienced improvements in LV ejection fraction by 4.5% (95% CI, 2.4 to 6.6), LV end systolic volume (LVESV) by -4.1 mL (95% CI, -9.0 to 0.8), LVESD by -1.7 mm (95% CI, -2.8 to -0.7), heart rate variability by 17 ms (95% CI, 6.5 to 28), and 6-minute walk distance by 56 m (95% CI, 37 to 75). Limitation of this study include the modest sample size, wide CIs of the estimated differences between left- and right-side VNS (clinically important differences could not be ruled out), and at least some of the clinical improvements were due to the placebo effect, especially in more subjective assessments. Further investigation is needed in a larger ~~randomized controlled trial~~RCT to confirm the results of this preliminary study.

Treatment of Other Conditions

Dawson and colleagues (2016) conducted a small randomized pilot study of implantable VNS in individuals with upper limb dysfunction after ischemic stroke. A total of 21 subjects were randomized to VNS plus rehabilitation or rehabilitation alone. The mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group versus +3.0 in the control group (p=0.064). Only 6 subjects in the VNS group achieved clinically meaningful response versus 4 subjects in the control group ~~(p=0.17)~~. Limitations of this study include the small sample size, lack of blinding to either the physiotherapist delivering the therapy or the subject, and no sham stimulation group.

Numerous small case series and retrospective studies of short duration have investigated implantable VNS therapy as treatment for essential tremor (Handforth, 2003), enhancing cognitive deficits in Alzheimer's disease (Merrill,

2006), anxiety disorders (George, 2008), and bulimia. Other review articles and studies explore the potential use of VNS in the treatment of acute asthma exacerbation (Miner, 2012; Yuan, 2015), autism (Danielsson, 2008), addictions, coma, pain syndromes (such as fibromylagia) (Lange, 2011), obesity-related food cravings in individuals with chronic TRD (Bodenlos, 2007), sleep disorders (such as narcolepsy), memory and learning deficits (Ansari, 2007), and severe refractory cluster or migraine headaches (Cecchini, 2009; Mauskop, 2005). A number of studies regarding VNS therapy are ongoing. To date, the FDA has not cleared the use of any type of implantable VNS device for these indications. Well-designed, ~~randomized clinical trials~~RCTs with larger sample populations are needed to demonstrate the safety and efficacy of implantable VNS therapy as a treatment for any of these conditions.

~~A search of the clinicaltrials.gov database identified studies in various phases investigating the effects of implantable VNS on conditions including, but not limited to, cluster headaches, active Crohn's disease despite treatment with a tumor necrosis factor (TNF) antagonist drug, myocardial function in heart failure, enteroendocrine secretion and glucose metabolism in Type 2 diabetes related obesity, rheumatoid arthritis, and recovery from minimally conscious or persistently vegetative states after traumatic brain injury (Shi, 2013) (U.S. National Institutes of Health [NIH], 2017). To date, the FDA has not cleared the use of any type of implantable VNS device for these indications. Well-designed, randomized clinical trials with larger sample populations are needed to demonstrate the safety and efficacy of implantable VNS therapy as a treatment for any of these conditions.~~

Non-Implantable Transcutaneous VNS (t-VNS or n-VNS)

Non-Implantable t-VNS for Cluster Headache

On May 30, 2017, the FDA cleared the gammaCore-S® non-implantable VNS device (EelectroCore® Medical, LLC, Basking Ridge, NJ) for the treatment of acute pain associated with cluster headache in adults. On November 27, 2018, the FDA expanded clearance to include adjunctive use for the preventive treatment of cluster headaches in adults. This non-invasive t-VNS therapy stimulates the cervical branch of the vagus nerve and is administered with a hand-held device that is approximately the size of a mobile phone. A conductive gel is applied on the stimulation surfaces of the device and it is placed on the neck. Each application takes approximately 2 minutes to administer, and more than one application may be required per treatment.

Nesbitt and colleagues (2015) conducted an observational study of the gammaCore t-VNS device for the treatment of cluster headaches. A total of 25 subjects were prescribed t-VNS treatment over 12 months with instructions to record their change in condition. A total of 6 subjects were excluded, leaving 19 subjects (11 with chronic cluster

headache and 8 with episodic cluster headache) in the final analysis. Subjects were administered up to 3 consecutive doses to treat an acute attack. For preventive use, they used 2-3 consecutive doses in the morning and late afternoon. A total of 15/19 subjects reported overall improvement with a mean overall self-estimated improvement of 48%. Prophylactic use significantly reduced the estimated mean attack frequency from 4.5/24 hours to 2.6/24 hours ~~(p<0.0005)~~. The researchers concluded that the study "provides Class IV evidence that for patients with cluster headache, transcutaneous stimulation of the vagus nerve aborts acute attacks and reduces the frequency of attacks."

Silberstein and colleagues (2016a) conducted a randomized, double-blind, sham-controlled prospective study (ACT1) evaluating t-VNS as acute treatment of cluster headache. Study participants were aged 18 to 75 years and were diagnosed with episodic cluster headache or chronic cluster headache according to the International Classification of Headache Disorders (ICHD)/International Headache Society (IHS) (2nd edition) criteria for ≥ 1 year before enrollment ~~*(Refer to the Background/Overview section, Cluster Headache, ICHD/IHS 3rd edition for descriptions of cluster headache, episodic cluster headache, and chronic cluster headache)*~~. A total of 150 participants were randomized (1:1) to receive t-VNS or sham treatment for ≤ 1 month during a double-blind phase; study completers could enter a 3-month t-VNS open-label phase. The primary endpoint was response rate, defined as the proportion of participants who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first cluster headache attack without rescue medication use through 60 minutes. Secondary endpoints included the sustained response rate (15-60 minutes). A total of 133 participants were included in the intention-to-treat population: all participants, 60 t-VNS-treated and 73 sham-treated; episodic cluster headache cohort: 38 t-VNS-treated, 47 sham-treated; and, chronic cluster headache cohort: 22 t-VNS-treated, 26 sham-treated. A response was achieved in 26.7% of t-VNS-treated participants and 15.1% of sham-treated participants (p=0.1). On subset analysis, response rates were significantly higher in the episodic cluster headache cohort treated with t-VNS than in the sham-treated cohort (t-VNS, 34.2%; sham, 10.6%~~; p=0.008~~), but not the chronic cluster headache cohort (t-VNS, 13.6%; sham, 23.1%~~; p=0.48~~). Sustained response rates were significantly higher with t-VNS for the episodic cluster headache cohort ~~(p=0.008)~~ and total population ~~(p=0.04)~~. A total of 35 of 150 participants reported adverse device effects (t-VNS, 11; sham, 24) in the double-blind phase and 18 of 128 participants in the open-label phase. Adverse device effects included application site reactions (such as burning, tingling, soreness, stinging or skin irritation, redness, or erythema), lip or facial drooping, pulling, or twitching, and dysgeusia or metallic taste. No serious adverse device effects were reported. In summary, participants with episodic cluster headache experienced clinical benefits in the t-VNS group over sham treatment, including rapid (within 15 minutes) and sustained (through 60 minutes) pain relief; although, significant treatment effects were not observed in participants with chronic cluster headache. In the final analysis, the response rate was not significantly different in t-VNS-treated versus sham-treated participants for the total study population.

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Goadsby and colleagues (2017) conducted a randomized, double-blind, sham-controlled prospective study (ACT2; NCT01958125) in four European countries at nine tertiary care sites, including academic medical centers and headache/pain/neurology clinics, comparing non-implantable t-VNS with a sham device for acute treatment of individuals with episodic cluster headache or chronic cluster headache. The trial consisted of a 1-week run-in period; a 2-week, randomized, double blind period during which participants were treated with either t-VNS or a sham device; and a 2-week, open label period where all participants received t-VNS therapy. In the run-in period, participants were allowed to maintain their standard of care regimens (that is, rescue treatments, medications, and/or inhaled oxygen). Participants collected data throughout the study using paper diaries to record all cluster headache attacks, including pain intensity at onset and at 15 and 30 minutes after initiation of stimulation, rescue treatment use, number of stimulations used, and adverse events. 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. A total of 48 t-VNS-treated (n=14 episodic cluster headache; n=34 chronic cluster headache) and 44 sham-treated (n=13 episodic cluster headache; n=31 chronic cluster headache) participants were included in the full data analysis set. For the primary endpoint, t-VNS (14%) and sham (12%) treatments were not significantly different in the total cohor~~t (p=0.71)~~t. In subgroup analysis, a significantly higher proportion of participants in the episodic cluster headache subgroup achieved pain-free status following treatment of attacks with t-VNS (48%) compared with sham treatment (6%~~; p<0.01~~). There was no significant treatment difference for this endpoint in the chronic cluster headache subgroup (t-VNS, 5%; sham, 13%~~; p=0.13~~). A total of 20 t-VNS-treated participants (40%) and 14 sham-treated participants (27%) had ≥ one adverse effect during the double-blind period, and 23 participants (23%) had ≥ one adverse effect during the open-label period. Limitations of this study include the short duration which did not allow for evaluation of continued/change in response with long-term t-VNS therapy and unequal number of participants in the cluster headache subtype groups, with less than 30% of participants comprising the episodic cluster headache group. In addition, during the open-label period, participants could alter their cluster headache treatment regimens by adding prophylactic therapies, or changing doses of existing treatments, or both, thus confounding the results and making it impossible to distinguish whether changes in efficacy outcomes were attributable to t-VNS therapy or to other changes in treatment during this period.

Gaul and colleagues (2016) reported the results of a prospective, randomized, open-label study (PREVA) of the gammaCore t-VNS device in the prophylactic treatment of chronic cluster headache. Participants aged 18 to 70 years were diagnosed with chronic cluster headache according to the ICHD/IHS (3rd edition) criteria for ≥ 1 year before enrollment The study included a 2-week baseline phase during which all participants received only their individualized standard of care (SoC) plan; a 4-week randomised phase during which participants were randomly assigned 1:1 by standard block design to receive either SoC plus t-VNS (prophylactic t-VNS; n=48) or SoC alone

(control; n=49); and an optional 4-week extension phase during which all participants received SoC plus t-VNS. The t-VNS prophylaxis treatment consisted of three 2-minute stimulations (i.e. three doses) 5 minutes apart administered twice daily (i.e. six doses per day) to the right side of the neck (right vagal nerve). The first prophylactic treatment was administered within 1 hour of waking; the second was administered 7 to 10 hours after the first treatment. If the cluster headache attack was not aborted within 15 minutes after stimulation, participants were instructed to take abortive medications (for example, subcutaneous sumatriptan, inhaled oxygen and intranasal zolmitriptan). The primary endpoint was the reduction in the mean number of cluster headache attacks per week. Response rate, abortive medication use and safety/tolerability were also assessed. At 4 weeks, the t-VNS group had a significantly greater reduction in the number of headaches than the control group, resulting in a mean therapeutic gain of 3.9 fewer headaches per week ~~(p=0.02)~~. The response rate, defined as a 50% or more reduction in cluster headaches, was 40% in the t-VNS group versus 8.3% in the control group ($p<0.001$). A total of 7 participants withdrew from the study due to adverse events; ~~only~~ two adverse events (depressed mood and cluster headache) occurred in more than 1 participant. During the 2 months of treatment, similar proportions of participants in the SoC plus t-VNS group (52%; 25 of 48) and control group (49%; 24 of 49) reported one or more adverse events; most adverse events were mild or moderate (93%; 108 of 116). Among participants assigned to SoC plus t-VNS, 38% (18 of 48) experienced adverse events during the randomized phase and 25% (12 of 48) experienced adverse events in the extension phase. Among participants assigned to control, 27% (13 of 49) experienced adverse events during the randomized phase and 24% (12 of 49) experienced adverse events in the extension phase. Overall, the most common adverse events in any treatment group were cluster headache attacks, headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain. Limitations of this study include the open-label design and lack of a sham placebo/control group which may have resulted in response to treatment in the placebo t-VNS group, the short duration of treatment, and use of participant-reported outcomes that have the potential to bias the results.

Gaul and colleagues (2017) conducted a post hoc analysis of the PREVA study using a modified intent-to-treat population, defined as participants who had available data for each study week. The number of participants in the modified intent-to-treat population varied among the endpoints (including time to and level of therapeutic response) due to dependence on the availability of measurable observations. Of the 92 participants who continued into the 4-week extension phase, 44 participants continued to receive t-VNS plus SoC and 48 participants switched from SoC alone to t-VNS plus SoC. The mean weekly attack frequency was significantly lower with t-VNS plus SoC than with SoC alone from week 2 of the randomized phase through week 3 of the extension phase ($p<0.02$). Attack frequencies in the t-VNS plus SoC group were significantly lower at all study time points than at baseline ~~($p<0.05$)~~. Attack frequencies were relatively stable throughout the extension phase. The global mean attack frequency at the end of the randomized phase had decreased by 40% from baseline in the t-VNS plus SoC group and had increased by 1% with SoC alone, representing a 41% therapeutic benefit of t-VNS ($p<0.001$). At the end of the randomized

phase, a significantly higher percentage of participants in the t-VNS plus SoC group than in the SoC group had ≥ 25%, ≥ 50%, and ≥ 75% attack frequency reductions from baseline ~~(≥ 25% and ≥ 50%, p<0.001; ≥ 75%, p=0.009)~~. Three participants (8%) in the t-VNS plus SoC group had a 100% attack frequency reduction; no participants in the SoC group had a 100% response. Safety and tolerability were as previously reported in the PREVA study, with similar proportions of participants in the t-VNS plus SoC and SoC groups reporting greater than or equal to one adverse event. Rates of discontinuation due to adverse events were also similar between groups. However, limitations of the PREVA study remain and future studies should address the issues documented earlier.

Marin and colleagues (2018) performed a multicenter, retrospective study of the gammaCore t-VNS device for individuals with cluster headaches. The researchers reviewed data from 30 subjects (29 with chronic cluster headaches and 1 with episodic cluster headaches) who used t-VNS after an inadequate response and/or intolerable side effects with ≥ 3 current or previous treatments. The subjects were instructed to use t-VNS for preventive therapy, acute therapy, or both. The mean duration of the evaluation period was 7.6 months (0.9-27.5). The mean range of attack frequency with SoC alone was 26.6 (3.8-77.0) attacks/week compared to 9.5 (0-38.5) with SoC plus t-VNS ($p<0.01$). A total of 3 subjects, who averaged 42 to 63 attacks/week before t-VNS, had no attacks during the evaluation period (range from 1.7 to 13.2 months). For the 25 subjects who reported duration of attacks, the mean decreased from 51.9 minutes with SoC alone to 29.4 minutes with SoC plus t-VNS ($p<0.01$). In the 18 subjects who reported severity, the mean decreased from 7.8 with SoC alone to 6.0 with SoC plus t-VNS ($p<0.01$). No serious adverse events were reported. The study was limited by a retrospective design and small sample. The researchers concluded that t-VNS "led to significant decreases in attack frequency, severity, and duration in patients with CH who previously did not benefit from or could not tolerate multiple preventive and/or acute treatments."

Non-Implantable VNS for Migraine Headaches

In addition to the FDA indications for cluster headaches, ~~On January 23, 2018, the FDA expanded the clearance of~~ the gammaCore device is FDA approved for the prevention and ~~to include the~~ acute treatment of ~~pain associated with~~ migraine headaches in both adolescents (age 12 and older) and adults.

Several small studies have evaluated the gammaCore device for migraine treatment and prophylaxis (Goadsby, 2014; Kinfe, 2015 [n=20 participants]). Goadsby and colleagues (2014) performed an open-label pilot study of portable t-VNS for the treatment of acute migraine with or without aura. A total of 27 from an initial sample size of 30 participants self-treated 80 migraine attacks (2 participants treated no migraine attacks with the device; 1 participant treated only an aura). Of the 54 moderate or severe attacks treated, 12 participants (22%) were pain free at 2 hours post treatment. Adverse events reported by 13 participants were all considered mild or moderate.

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~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. . The member's contract benefits in effect on the date that services are rendered must be used. . Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. . Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

In an open-label, single-arm, multicenter study, Barbanti and colleagues (2015) evaluated the effects of the gammaCore t-VNS device for high-frequency episodic migraine (HFEM) and chronic migraine (CM). A total of 50 subjects (HFEM n=14; CM n=36) were enrolled, and 131 attacks were analyzed. Exclusion criteria included those with a history of cerebrovascular, cardiovascular, atherosclerotic, or significant neurological disease. Also excluded were those with significant systemic disorders or implanted electrical devices. Subjects were instructed to use t-VNS to self-treat up to three migraine attacks that occurred over 2 weeks. For each migraine, subjects delivered two doses at 3 minutes intervals within 20 minutes of mild or moderate pain onset. Subjects were allowed to take rescue medication if they had no reduction in pain within 2 hours. They rated their pain using a visual analog scale (VAS) and recorded symptoms and adverse events. Pain relief was defined as a ≥ 50% reduction in VAS score, and pain-free was defined as a VAS score of 0. The primary end-point was pain-free status at 2 hours. At the end of the evaluation period, 27/48 subjects (56.3%) reported pain relief at 1 hour, including 17 subjects (35.4%) who were pain free. At 2 hours, 31 subjects (64.6%) reported pain relief, including 19 (39.6%) who were pain free. When all attacks were combined (n=131), the pain-relief rate was 38.2% at 1 hour and 51.1% at 2 hours. For all combined attacks, the pain-free rate was 17.6% at 1 hour and 22.9% at 2 hours. Rescue medications were taken in 53.4% (70/131) of the attacks. The researchers noticed that t-VNS was more effective in those with HFEM than CM. No major adverse events were reported. The study was limited by the open-label design, short duration, and lack of a control group. The authors concluded that t-VNS was able to achieve pain relief without serious side effects. They recommend larger studies to confirm their findings.

Silberstein and colleagues (2016b) evaluated the feasibility, safety, and tolerability of t-VNS in a prospective, multicenter, double-blind, sham-controlled pilot study of t-VNS for the prevention of chronic migraine attacks in adults (EVENT study). A total of 59 participants (mean age, 39.2 years) with chronic migraine (15 headache days/month; mean headache frequency, 21.5 days/month) entered the baseline phase (1 month) and were subsequently randomized to t-VNS or sham treatment (2 months) before receiving open-label t-VNS treatment (6 months). The primary endpoints were safety and tolerability. Efficacy endpoints in the intent-to-treat population included change in the number of headache days per 28 days and acute medication use. During the randomized phase, tolerability was similar for t-VNS (n=30) and sham treatment (n=29). Most adverse events were mild or moderate and transient (upper respiratory tract infections and gastrointestinal symptoms). Mean changes in the number of headache days were -1.4 (t-VNS) and -0.2 (sham) (p=0.56). A total of 27 participants completed the open-label phase. For the 15 completers initially assigned to t-VNS, the mean change from baseline in headache days after 8 months of treatment was -7.9 (95% CI, -11.9 to -3.8; p<0.01). Limitations of this study include the small sample size and high discontinuation rate. The investigators noted that blinding to active or sham treatment

was "challenging, especially in comparison with drug studies." In addition, the missing data and high discontinuation rates occurring disproportionately across treatment groups could affect study outcomes.

The FDA approval of the gammaCore t-VNS device for migraines was based on the "Prospective Study of nVNS for the Acute Treatment of Migraine (PRESTO)" randomized sham-controlled trial (Tassorelli, 2018). A total of 248 subjects with episodic migraines (with or without aura) were randomized to receive t-VNS (n=120) or sham treatment (n=123) within 20 minutes of pain onset, with a repeat treatment available if the pain had not improved in 15 minutes. Inclusion criteria included subjects 18-75 years old, a diagnosis of migraine based on ICHD-3 beta criteria, < 50 years old at migraine onset, and attack frequency of 3-8 attacks a month with < 15 headache days per month over the last 6 months. Subjects on migraine medication were required to have a stable dose and frequency schedule 2 months before the study, and subjects could not start new medications during the study. Device training was provided to the subjects by an unblinded trainer; subjects and investigators were blinded prior to and during the study for the primary endpoint. The primary endpoint was the proportion of subjects who were pain-free up to 120 minutes after a first attack without using medication. Pain was defined according to the IHS guidelines. After the first treated migraine attack, the proportion of subjects in the t-VNS group who were pain-free was significantly higher at 30 and 60 minutes but not at 120 minutes. However, a post-hoc repeated measures test found t-VNS to be superior to sham for the pain-free outcome through 30, 60, and 120 minutes (odds ratio [OR] 2.3; 95% CI, 1.2 to 4.4; p=0.012). The most common adverse events were application site discomfort and nasopharyngitis; no serious adverse events were reported. The researchers concluded that the study demonstrates "the efficacy of nVNS for aborting attacks as early as 30 minutes and up to 60 minutes and for relieving pain at 120 minutes in the acute treatment of episodic migraine with or without aura." These findings only represent the 8-week study period. Further studies with long-term follow-up are needed to evaluate safety and efficacy for a therapy intended to be used as a long-term therapy in a chronic condition.

Grazzi and colleagues (2018) performed a post-hoc analysis of the PRESTO trial to determine the ability of gammaCore to consistently deliver clinically meaningful improvements in pain intensity while reducing the need for rescue medication. The primary end point was the percentage of subjects with a ≥ 1-point reduction in pain intensity on a 4-point scale, with 0 being no pain and 3 being severe pain. Pain was measured at 30, 60, and 120 minutes after the first treated attack. Compared to sham (n=123), there was a significantly higher percentage of individuals who used acute t-VNS treatment (n=120) that reported a ≥ 1-point reduction in pain intensity at 30 minutes (t-VNS, 32.2%; sham, 18.5%; p=0.020), 60 min (t-VNS, 38.8%; sham, 24.0%; p=0.017), and 120 min (t-VNS, 46.8%; sham, 26.2%; p=0.002) after the first attack. The number of subjects who did not require rescue medication was significantly higher in the t-VNS group compared to sham for the first attack (t-VNS, 59.3%; sham, 41.9%; p=0.013) and all attacks (t-VNS, 52.3%; sham, 37.3%; p=0.008). Differences in pain-free rates between t-

VNS and sham were more pronounced in subjects who initiated treatment when their attack was mild than for those who waited until the pain was moderate or severe. When initial pain intensity was mild, the percentage of subjects with no pain after treatment was significantly higher with t-VNS than with sham at 60 min (all attacks: t-VNS, 37.0%; sham, 21.2%; p=0.025) and 120 min (first attack: t-VNS, 50.0%; sham, 25.0%; p=0.018; all attacks: t-VNS, 46.7%; sham, 30.1%; p=0.037). The researchers concluded that t-VNS "has the flexibility to be used alone or as adjunctive therapy for multiple attacks without risk of pharmacologic interactions and adverse events."

Martelletti and colleagues (2018) published additional findings from the PRESTO trial. They found that the t-VNS group (n=120) had a significantly greater percentage of attacks treated during the double-blind period that were pain-free at 60 minutes and 120 minutes compared to the sham group (n=123). The t-VNS had significantly greater decreases from baseline for the first attack and all attacks. For individuals in the t-VNS group that were pain-free at 120 minutes, > 75% remained pain-free at 24 hours. While these additional secondary endpoints are promising, the analysis is limited by the retrospective design, and further studies are needed to confirm the results.

Diener and associates (2019) evaluated the use of non-invasive vagus nerve stimulation in the prevention of episodic migraine. The PREMIUM trial is a phase 3, prospective, multicentre, double-blind, sham-controlled, randomized trial intended to evaluate efficacy, tolerability and safety using an intent-to-treat (ITT) population. Adults age 18 to 75 with a history of migraines who experienced 5-12 migraine days per month in the past 4 months, with at least 2 migraines lasting more than 4 hours, were eligible to participate. Participants were randomized to receive the GammaCore VNS device (n=169) or a sham device (n=172). The sham device produced a low-frequency biphasic direct current signal, which was intended to be perceived by the user but did not stimulate the vagus nerve or contract the muscle. Preventive treatment involved administering 2 consecutive bilateral stimulations 3 times a day. The study began with a 4-week run-in period of no study treatment, a 12-week period of use of either the VNS or sham device, followed by a 24-week open label period of VNS. The primary endpoint was mean reduction in number of migraine days per month. The use of the VNS device was not shown to be superior to the use of the sham device. Following the blinded portion of the study, the ITT population reported migraine reductions of -2.26 days in the VNS device group and -1.80 days in the sham device group (p=0.15). The authors noted that treatment responses to the VNS device (migraine and headache days) were maintained during the open-label period. The study had several limitations, including suboptimal adherence to the treatment protocol in both groups, and a significant drop-out rate among participants. The authors noted that the sham device was not inert, providing some vagus nerve stimulation which might have decreased the therapeutic gain in the VNS device group. Finally, the daily treatment protocol required bilateral stimulations, which authors noted could have mitigated the overall efficacy of the device.

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Other Considerations

The American Headache Society (Robbins, 2016) has published evidenced-based guidelines on the treatment of cluster headache. The guideline, reviewing outcomes of the PREVA study (Gaul, 2016), considers t-VNS to be a "novel" neurostimulation device in the treatment of cluster headache; however, the "therapeutic flexibility" of t-VNS "does not appear to be effective in the acute treatment of cluster headache (CH)…" In summary, the guideline suggests that "future studies that are blinded with a sham control are warranted to elucidate the efficacy and safety of noninvasive vagus nerve stimulation for treatment of CH."

~~In an expert panel review of gammaCore for cluster headaches (Silberstein, 2017), a group of nine medical experts concluded that gammaCore should be offered as a first-line treatment for episodic cluster headaches.~~

Non-Implantable t-VNS for Other Conditions

Other t-VNS devices have been developed to transcutaneously stimulate the vagus nerve for the treatment of conditions including epilepsy, depression, migraine headache, impaired glucose tolerance, schizophrenia, and tinnitus. One device, the transcutaneous VNS System (t-VNS®) with *NEMOS*® (CerboMed GmbH, Erlangen, Germany) received European clearance (CE mark) in 2011 for treatment of drug-resistant epilepsy. This device uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Device users self-administer electrical stimulation for several hours a day; no surgical procedure is required. The device received the CE mark in Europe in 2011, but has not received FDA 510(k) clearance for use in the United States. Other studied transcutaneously-applied auricular VNS devices include, but are not limited to, the TENS-200 and TENS-220 (Hua Tuo, Suzhou, China) and the Tinnoff Profiler (Tinnoff, Inc., Helsinki, Finland).

To date, the FDA has not cleared or approved any non-implantable t-VNS device for use in the treatment of any of the following conditions.

Pharmacoresistant Epilepsy

The safety and effectiveness of non-implantable, t-VNS therapy has been investigated for the treatment of individuals with chronic, drug-resistant epilepsy. He and colleagues (2013) conducted a small pilot study of 14 children with intractable epilepsy using an auricular t-VNS device (TENS-200) for 24 weeks as an adjunct to their current medication regimen. The mean reduction in seizure frequency from baseline through week 8, weeks 9

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through 16, and weeks 17 through 24 was 31.8%, 54.13%, and 54.2%, respectively. The investigators found no correlation between the therapeutic efficacy of t-VNS and baseline seizure frequency reduction. In addition, neither age, gender, nor seizure syndrome predicted response to the device. In terms of reported side effects, t-VNS was well tolerated and only 2 participants reported mild ulceration of the skin at the stimulation area. Limitations of this study include the small sample size and lack of a control group.

Stefan and colleagues (2012) evaluated t-VNS therapy (using an unspecified CerboMed device) in a small case series of 10 adults with drug-resistant epilepsy. Stimulation via the auricular branch of the vagus nerve of the left tragus was delivered 3 times per day for 9 months. Subjective documentation of stimulation effects was obtained from self-reported seizure diaries. An assessment of seizure frequency was evaluated with prolonged outpatient video electroencephalography (EEG) monitoring. Other evaluations included computerized testing of cognitive, affective, and emotional functions. Three participants withdrew from the study with 5 of the remaining 7 participants reporting an overall reduction of seizure frequency after 9 months of t-VNS. A major discrepancy was noted, however, between subjective reports of seizure activity and quantified video-EEG in 2 participants. One participant reported a 37% reduction of seizure frequency (baseline: 21 seizures per week; average of months 7 to 9: 13.3 seizures per week) but an increase in seizures was recorded during outpatient video-EEG monitoring. A second participant reported a significant increase in simple partial seizures with subjective signs (baseline: 1.6 seizures per week; average of months 7 to 9: 4.2 per week), but no changes were seen on EEG recording. Non-implantable t-VNS was well-tolerated with side effects limited to hoarseness, headache or obstipation. Limitations of this study include the small sample size and lack of a randomized control group.

Aihua and colleagues (2014) reported results from a case series of 60 individuals with pharmacoresistant epilepsy treated with a t-VNS device (TENS-200). A total of 60 participants were equally randomized to receive either stimulation over the earlobe (control group) or the Ramsay-Hunt zone, which includes the external auditory canal and the conchal cavity and is considered to be the somatic sensory territory of the vagus nerve. Four participants from the treatment group and 9 participants from the control group were excluded from analysis due to loss to follow-up (n=3, treatment group; n=2, control group); adverse effects (n=1, treatment group), or increase or lack of decrease in seizures or other reasons (n=7, control group). Compared with baseline, the median monthly seizure frequency in the treatment group was significantly reduced after 6 months (5.5 versus 6.0; p<0.001) and 12 months (4.0 versus 6.0; p<0.001) of t-VNS therapy. However, the median seizure frequency in the treatment group was not significantly lower than that in the control group until 12 months of treatment (4.0 versus 8.0; p<0.001). Limitations of this study include the small sample size, potential for unblinding in the control group as participants brought the instruments home for daily use and may have realized that they were in sham stimulation, and the study focused on seizure frequency with no comparison of different seizure syndromes.

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Shiozawa and colleagues (2015) published the results of a systematic review of the peer-reviewed medical literature through 2013 evaluating the clinical utility of t-VNS and trigeminal nerve stimulation. Three t-VNS clinical trials assessed physiological features (that is, brain activation patterns and pain thresholds) in healthy volunteers, and one trial evaluated use in individuals with pharmacoresistant epilepsy. One study was a crossover design and the remaining trials were open-label studies. This analysis was limited in drawing conclusions due to lack of standardization of study design and small study populations (n=84). The authors concluded that controlled trials measuring long-term outcomes are required before drawing conclusions concerning the clinical utility of t-VNS to improve health outcomes for any condition.

Bauer and colleagues (2016) performed a randomized, two-arm, parallel group, prospective, double-blind, controlled clinical trial (cMPsE02) at nine sites in Germany and one site in Austria to assess the efficacy and safety of t-VNS (using the *NEMOS* device) compared with control stimulation in individuals with drug-resistant epilepsy. Individuals were eligible for study participation if they had a history of greater than or equal to three focal and/or generalized seizures per month, not more than 21 consecutive seizure-free days, and on a stable regimen of less than or equal to three antiepileptic drugs for at least 5 weeks prior to study enrollment and maintained this drug regimen throughout the study. Following an 8-week baseline period during which seizure rate was self-documented in a diary, 76 participants were randomized in a 1:1 ratio to treatment with either active t-VNS (that is, 25 Hz stimulation frequency, 250 µs pulse width, 30 s on/30 s off) or low level (active control, 1 Hz stimulation frequency, 250 µs pulse width, 30 s on/30 s off) t-VNS for 4 hours daily for 20 weeks. Two baseline visits (weeks 0 and 4) and 7 treatment visits (weeks 8, 9, 12, 16, 20, 24, 28) were performed. The primary objective was to demonstrate superiority of add-on therapy with t-VNS (stimulation frequency 25 Hz, n=39) versus active control (1 Hz, n=37) in reducing seizure frequency over 20 weeks. The investigators reported that treatment adherence was 84% in the 1 Hz group and 88% in the 25 Hz group, respectively. A total of 58 participants (76%) completed the study; 8 participants in the 1 Hz group and 10 participants in the 25 Hz group prematurely discontinued the study. The mean seizure reduction per 28 days at end of treatment as compared to baseline was -2.9% in the 1 Hz group and 23.4% in the 25 Hz group (p=0.146). For those individuals in the 25 Hz group who completed the full treatment period, a significant reduction in seizure frequency occurred in comparison to the control group (20 weeks; n=26, 34.2%; p=0.034). Responder rates (25%, 50%) were similar in both groups. On subgroup analyses, no significant differences were reported for seizure type and baseline seizure frequency. Any self-reported adverse events were mild or moderate and consisted of headache, ear pain, application site erythema, vertigo, fatigue, and nausea. Four serious adverse events were reported, including one sudden unexplained death in the 1 Hz group which was assessed as not treatment -related. According to the investigators, the most relevant limitation of this study is that stimulation intensity was significantly higher in the 1 Hz group as compared to the 25 Hz group, "which may have

reduced the difference in treatment efficacy between both groups." Approximately one-third of study participants were not on any anticonvulsant medication, which is an unusually high rate and may limit generalizability of the results. Finally, the collection of data in self-maintained participant diaries may limit the accuracy of seizure quantification by some participants.

Schizophrenia

Hasan and colleagues (2015) conducted a bicentric randomized, sham-controlled, double-blind pilot study of the safety and efficacy of t-VNS (CM02 device, CerboMed GmbH, Erlangen, Germany) in 20 individuals with stable schizophrenia. Participants in the active t-VNS group received daily active stimulation of the left auricle for 26 weeks. The sham t-VNS group received daily sham stimulation for 12 weeks followed by 14 weeks of active stimulation. The primary outcome was defined as a change in the Positive and Negative Symptom Scale (PANSS) total score between baseline and week 12. In the intention-to-treat analysis from week 12 to week 26, the PANSS total scores were reduced by 8.5 (± 5.3) in the active t-VNS group and 5.1 (± 3.7) in the sham t-VNS group (switched to active treatment after week 12), with no significant differences between groups (p=0.52). The treatment was well tolerated with no significant adverse effects associated with use of the t-VNS device beyond local skin irritation or mild pain. The investigators concluded that "neither psychopathological and neurocognitive measures nor safety measures showed significant differences between study groups"; however, further study of overall patterns of symptom change with use of t-VNS may be warranted in the treatment of individuals with schizophrenia.

Tinnitus

Kreuzer and colleagues (2014) reported the results of a single-arm pilot study of t-VNS with two different devices (CerboMed CM02 and *NEMOS*) for the treatment of tinnitus. A total of 48 participants were included in the primary intention-to-treat analysis. The primary outcome was a change in mean Tinnitus Questionnaire (TQ) score from baseline to 6-month follow-up, for the 24 participants in the first phase of the study who used an earlier generation t-VNS device. For these participants, the TQ total score decreased by 3.7 points (p=0.036). A total of 9 participants (37.5%) were considered responders. In the second phase of the study, 24 participants who used the next generation t-VNS device reported a decrease by 2.8 points (p=0.014) in the mean TQ score. Eleven participants were considered responders (45.8%). A per-protocol analysis of 28 participants who received treatment reported no significant improvement in TQ scores. The authors concluded that t-VNS treatment did not result in clinically significant improvement in tinnitus complaints.

Lehtimaki and colleagues (2013) evaluated the effect of auricular t-VNS in a pilot trial combining t-VNS (Tinnoff Profiler) with sound therapy to reduce the severity of tinnitus and tinnitus-associated distress. Limitations of this study are the small sample size (n=10) and use of concomitant sound therapy.

Other Conditions

Huang and colleagues (2014) reported results of a pilot ~~randomized controlled trial~~RCT of a t-VNS device (TENS-200) that provided auricular stimulation for the treatment of impaired glucose tolerance. A total of 70 participants were randomized to active or sham t-VNS, along with 30 controls who received no t-VNS treatment. After 12 weeks of treatment, participants who received active t-VNS were reported to have significantly lower 2-hour glucose tolerance test results than those who received sham t-VNS (7.5 versus~~.~~ 8 mmol/L; p=0.004).

Other studies evaluating the effect of auricular t-VNS include a non-randomized pilot study using t-VNS for mild to moderate major depressive disorder (Rong, 2016) and a small, randomized crossover study (n=48; Busch, 2013) investigating whether t-VNS (STV02, CerboMed GmbH, Erlangen, Germany) may have the potential to alter pain perception and sensitivity during sustained application of painful heat. A search of the ClinicalTrials.gov database has identified trials in various phases evaluating non-implantable t-VNA for the treatment of cluster headaches, tinnitus, pain perception in pain syndromes, schizophrenia, and evaluation of anti-inflammatory markers in individuals with juvenile idiopathic arthritis.

Background/Overview

Epilepsy

The Centers for Disease Control and Prevention (CDC, 2020~~19~~) estimates about 3 million adults and 470,000 children in the United States population in 2015 had active epilepsy. New cases of epilepsy are most common among children and older adults. According to the National Institute of Neurological Disorders and Stroke (NINDS, 2017) about 70% of individuals diagnosed with epilepsy experience seizures that can be controlled with medication and surgical techniques. The American Association of Neurological Surgeons (AANS, 2013) currently classifies seizures into two basic categories: primary generalized seizures and focal seizures (previously referred to as partial seizures). Classifying the type of seizure is important in the selection of appropriate antiepileptic drug treatment. Despite advances in the medical and surgical treatment of epilepsy, 25% to 50% of individuals with epilepsy experience breakthrough seizures or suffer from debilitating adverse effects of antiepileptic drugs.

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Implantable VNS

An implantable VNS device is similar to a cardiac pacemaker and includes a generator device surgically placed under the skin in the left chest area, typically below the collarbone. A nerve stimulation electrode is tunneled under the skin to the lower neck where it is placed around the left cervical vagus nerve. Using an external programmer the stimulation parameters of the device are set (or reset) to deliver preprogrammed intermittent electrical pulses to the vagus nerve, which then transmits the stimulation to the brain to create widespread antiepileptic effects. Additionally, an individual can activate the system when sensing the onset of a seizure to deliver an additional dose of stimulation by passing a magnet over the area of the chest where the device is implanted. The device is powered by a lithium thionyl chloride battery that must be replaced every 1.5-5 years depending on the stimulation parameters.

Reports of adverse effects of implantable VNS therapy have included voice alteration, headache, neck pain, cough, and obstructive or central sleep apnea (CSA)/sleep breathing disorders; however, "the mechanism for CSA seen in patients with a vagus nerve stimulator is not fully known" (Forde, 2017). In a review article, Giordano and colleagues (2017) report on surgical techniques for VNS implantation and related acute and delayed morbidity. Late complications of VNS therapy, related to the device and to stimulation of the vagus nerve include, but are not limited to, delayed arrhythmias, laryngopharyngeal dysfunction (hoarseness, dyspnea, and coughing), obstructive sleep apnea, stimulation of the phrenic nerve, and tonsillar pain mimicking glossopharyngeal neuralgia. Complete surgical removal or revision and replacement of the device is considered in cases of device malfunction (4%-16.8%), failure of VNS therapy, intolerable side effects, or resulting from the individual's specific request. Sleep breathing disorders and laryngeal motility alterations are reported in numerous single and small case series of individuals implanted with VNS for drug-resistant epilepsy. In a retrospective case series, Zambrelli and colleagues (2016) evaluated 23 individuals with medically refractory epilepsy who underwent sleep testing before and after VNS implantation. A total of 18 individuals underwent endoscopic laryngeal examination post-VNS implantation. Statistical analysis was carried out to assess an association between laryngeal motility alterations and the onset/worsening of sleep breathing disorders. After VNS implantation, 11 individuals showed new-onset of mild/moderate sleep breathing disorders. Individuals already affected by obstructive sleep apnea showed worsening of sleep breathing disorders, and those with new-onset obstructive sleep apnea had a laryngeal pattern with left vocal cord adduction (LVCA) during VNS stimulation. The authors suggest there is an association between VNS and sleep breathing disorders that should be investigated in individuals before and after VNS implantation.

The automated stimulation function of a closed loop VNS model detects heart rate changes and automatically responds by sending a programmed stimulation to the vagus nerve. Cardiac signal changes have been evaluated as a potential biomarker that might indicate the ictal onset of epileptic seizures. Approximately 82% of individuals with epilepsy had at least one seizure associated with significant heart rate increases, which occur in the pre-ictal phase (Eggleston, 2014). The AspireSR or SenTiva devices were developed to take advantage of this extra-cerebral indicator of ictal onset and preemptively prevent seizures.

Non-Implantable VNS

A non-implantable VNS device (also referred to as transcutaneous VNS [t-VNS] or n-VNS) requires no surgical procedure. Auricular t-VNS devices combine a stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve via skin over the concha of the ear. Another t-VNS device stimulates the cervical branch of the vagus nerve with a handheld device. Device users self-administer electric stimulation using prespecified device parameters agreed upon by the prescribing physician. Side effects of t-VNS are similar to those reported with an implantable VNS device, in addition to local skin irritation at the site of application.

Definitions

Focal seizure: A seizure that begins with an electrical discharge in a relatively small area (called the focus) of the brain; previously referred to as a partial or localization-related seizure. In most cases, the cause is unknown, but may be related to a brain infection, head injury, stroke, or a brain tumor.

International Classification of Headache Disorders (ICHD): Classification and diagnostic criteria of headache disorders published by the International Headache Society (IHS) and incorporated into the 10th edition of the International Classification of Diseases (ICD-10).

Medically refractory seizures: Seizures that occur despite treatment with therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse side effects.

Migraine headache: A vascular headache believed to be caused by blood flow changes and certain chemical changes in the brain leading to a cascade of events that include constriction of arteries supplying blood to the brain that result in severe head pain, stomach upset, and visual disturbances.

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~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. . The member's contract benefits in effect on the date that services are rendered must be used. . Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. .Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~

Refractory depression: A major depressive disorder that fails to demonstrate an adequate response to an adequate treatment trial of antidepressant medications (i.e. sufficient intensity of treatment for sufficient duration); also referred to as treatment-resistant depression (TRD). Potential factors contributing to apparent non-response include trial adequacy, individual compliance, differential diagnosis, and treatable comorbid conditions.

Vagus nerve: A nerve that controls both motor and sensory functions of the gastrointestinal tract, heart and larynx; also referred to as the 10th cranial nerve.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when specified as vagus nerve stimulator and criteria are met:

CPT	
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional

HCPCS

C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension

ICD-10 Procedure

00HE0MZ	Insertion of neurostimulator lead into cranial nerve, open approach
00HE3MZ	Insertion of neurostimulator lead into cranial nerve, percutaneous approach
00HE4MZ	Insertion of neurostimulator lead into cranial nerve, percutaneous endoscopic approach

ICD-10 Diagnosis

G40.001-G40.919	Epilepsy and recurrent seizures

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when specified as vagus nerve stimulator when criteria are not met or for all other diagnoses (including but not limited to those listed below), or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

ICD-10 Diagnosis

	All other diagnoses, including, but not limited to:
E66.01-E66.9	Overweight and obesity

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F30.10-F39	Mood (affective) disorders
F50.2	Bulimia nervosa
F84.0	Autistic disorder
G25.0-G25.2	Essential and other specified forms of tremor
G30.0-G30.9	Alzheimer's disease
G43.001-G43.919	Migraine
G43.A0-G43.D1	Migraine
G44.001-G44.029	Cluster headaches
G47.00-G47.9	Organic sleep disorders
G80.0-G80.9	Cerebral palsy
G89.0	Central pain syndrome
G89.4	Chronic pain syndrome
I50.1-I50.9	Heart failure
J45.20-J45.998	Asthma
K50.00-K50.919	Crohn's disease (regional enteritis)
M79.7	Fibromyalgia
R63.2	Polyphagia

When services are also Investigational and Not Medically Necessary:

HCPCS

E1399	Durable medical equipment, miscellaneous [when specified as a transcutaneous (non-implantable) VNS device]
K1020	Non-invasive vagus nerve stimulator

ICD-10 Diagnosis

	All diagnoses

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1. Aaronson ST, Carpenter LL, Conway CR, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. Brain Stimul. 2013; 6(4):631-640.

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   - Lennox-Gastaut Syndrome.

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t-VNS System with *NEMOS*
VNS Therapy

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	05/13/2021	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
	04/01/2021	Updated Coding section with 04/01/2021 HCPCS changes; added K1020.
Revised	05/14/2020	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Added a requirement to the revision/replacement language that current device is not functioning properly. Updated Rationale, Description and References sections.
Reviewed	11/07/2019	MPTAC review. Rationale, Definitions, References, and Websites sections updated. Updated Coding section; added C1778.
Reviewed	01/24/2019	MPTAC review. Rationale, Background, References, and Websites sections updated.
	12/27/2018	Updated Coding section with 01/01/2019 CPT changes; added 95976. 95977; removed 95974, 95975 deleted 12/31/2018.
Reviewed	02/23/2018	Behavioral Health Subcommittee review.
Reviewed	01/25/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, Background, References, and Websites for Additional Information sections.
Revised	08/03/2017	MPTAC review. Added a MN statement for replacement or revision of an implanted neurostimulator pulse generator system (with or without lead changes) for medically and surgically refractory seizures when the MN criteria are met. Added an INV & NMN statement for replacement or revision of an implanted neurostimulator pulse generator system (with or without lead changes) when the medically necessary criteria for device implantation are not met. Clarified the INV& NMN statement for use of t-VNS as acute or preventive treatment for specific types of headaches. Updated Rationale, Background, References, Websites for Additional Information, and Index sections.

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Revised	02/02/2017	MPTAC review.
Revised	01/20/2017	Behavioral Health Subcommittee review. Updated formatting in Position Statement section. Clarified the INV & NMN statements. Updated Rationale, Background, References, and Websites for Additional Information sections.
Revised	02/04/2016	MPTAC review. Added use of implantable VNS as investigational and not medically necessary for the treatment of asthma and pain syndromes. Added headaches (including cluster and migraine headaches), pain syndromes, schizophrenia, and tinnitus to the investigational and not medically necessary statement for use of non-implantable VNS.
Revised	01/29/2016	Behavioral Health Subcommittee review. Updated cross-reference in the Description. Added use of implantable VNS as investigational and not medically necessary for the treatment of asthma and pain syndromes. Added headaches (including cluster and migraine headaches), pain syndromes, schizophrenia, and tinnitus to the investigational and not medically necessary statement for use of non-implantable VNS. Updated Rationale, Coding, References, and Websites for Additional Information sections.
Revised	11/05/2015	MPTAC review. Updated Description, adding a cross-reference to SURG.00024 Surgery for Clinically Severe Obesity which addresses the use of vagal nerve blocking therapy (VBLOC) for the treatment of morbid obesity. Added use of VNS as investigational and not medically necessary for the treatment of Crohn's disease. Clarified use of VNS therapy as investigational and not medically necessary for obesity-related food cravings. Updated Rationale, Background, References, Websites for Additional Information, and Index sections. Updated Coding section to remove codes 0312T-0317T no longer addressed in this document, and removed ICD-9 codes.
Reviewed	02/05/2015	MPTAC review.
Reviewed	01/30/2015	Behavioral Health Subcommittee review. Minor format changes and updates to Rationale, References and Websites for Additional Information sections.
Revised	08/14/2014	MPTAC review. Expanded scope of document, adding a separate investigational and not medically necessary statement for non-implantable VNS for all behavioral health and medical indications. Clarified investigational and not medically necessary statement for implantable VNS. Updated Description, Rationale, Background, Coding, References, Websites for Additional Information, and Index sections.

Revised	08/08/2014	Behavioral Health Subcommittee review. Expanded scope of document, adding a separate investigational and not medically necessary statement for non-implantable VNS for all behavioral health and medical indications. Clarified investigational and not medically necessary statement for implantable VNS. Updated Description, Rationale, Background, Coding, References, Websites for Additional Information, and Index sections.
	01/01/2014	Updated Coding section with 01/01/2014 HCPCS changes.
Revised	08/08/2013	MPTAC review. Added treatment of heart failure to the VNS investigational and not medically necessary indications and clarified electronic analysis statement. Updated Rationale, Background, Definitions, Coding, References, Websites for Additional Information, and Index sections.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes.
Reviewed	08/09/2012	MPTAC review.
Reviewed	08/03/2012	Behavioral Health Subcommittee review. Updated Rationale, Background, References, and Websites for Additional Information.
Reviewed	11/17/2011	MPTAC review. Updated Rationale, References, and Websites for Additional Information.
Revised	11/18/2010	MPTAC review. Clarified statement for electronic analysis of an implanted VNS device, that it is medically necessary for monitoring of an appropriately implanted device. Updated the Rationale, Background, Definitions, References, Websites for Additional Information and Index~~.~~ . Updated Coding section to include 01/01/2011 CPT changes; removed 64573 deleted 12/31/2010.
Revised	11/19/2009	MPTAC review. Added medically necessary statement addressing analysis of an implanted neurostimulator pulse generator system for VNS when criteria are met. Clarified and expanded investigational and not medically necessary statements: added specific medical conditions and separate statement to address when analysis of an implanted neurostimulator pulse generator system for VNS is investigational and not medically necessary. Updated Description, Rationale, Background, and References. Updated Coding section with 01/01/2010 HCPCS changes.
Reviewed	11/20/2008	MPTAC review. Rationale, Definitions, and References updated.
	10/01/2008	Updated Coding section with 10/01/2008 ICD-9 changes.

Reviewed	11/29/2007	MPTAC review. Clarified Position Statement. Rationale, Background, Coding and References updated. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary."
Reviewed	12/07/2006	MPTAC review. Background/Overview updated~~—~~.
Reviewed	09/14/2006	MPTAC review. References updated. Coding update: removed HCPCS E0752, E0754, E0756 deleted 12/31/05.
	01/01/2006	Updated Coding section with 01/01/2006 CPT/HCPCS changes
Revised	12/01/2005	MPTAC review.
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD).
Revised	09/22/2005	MPTAC review.
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	01/28/2004	SURG.00007	Vagus Nerve Stimulation Therapy
WellPoint Health Networks, Inc.	04/28/2005	2.10.05	Vagus Nerve Stimulation

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~~Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. . The member's contract benefits in effect on the date that services are rendered must be used. . Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. .Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.~~