Vagus Nerve Stimulation

Effective: January 1, 2024

Next Review: April 2024
Last Review: December 2023

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Vagus nerve stimulation (VNS) involves implantation of an infraclavicular pulse generator that sends weak electric impulses to the left vagus nerve within the carotid sheath in the neck. Transcutaneous (nonimplantable) vagus nerve stimulation has also been proposed as a treatment of a number of conditions.

MEDICAL POLICY CRITERIA

Note: This policy does not apply to vagus nerve **blocking** therapy. See Cross References.

I. Implantable vagus nerve stimulation (VNS) may be considered **medically necessary** as a treatment of medically refractory seizures. Patients must have tried and been unresponsive to or intolerant of at least two antiepileptic drugs.

II. Revision(s) to an existing stimulator may be considered **medically necessary** after the device has been placed.

III. The replacement of all or part of an existing stimulator and/or generator is considered **medically necessary** when the existing stimulator and/or generator is malfunctioning, cannot be repaired, and is no longer under warranty.

IV. Replacement of all or part of an existing stimulator and/or generator is considered **not medically necessary** when Criterion III. is not met.

V. Implantable VNS is considered **investigational** when Criterion I. is not met and for all other indications, including but not limited to essential tremors.

VI. Transcutaneous and non-implantable vagus nerve stimulation devices are considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Current Symptomology
- Antiepileptic medications given and response

CROSS REFERENCES

1. Gastric Electrical Stimulation; Surgery, Policy No. 111
2. Responsive Neurostimulation, Surgery, Policy No. 216

BACKGROUND

An implanted VNS device delivers mild electronic impulses via two electrodes connected to the generator and wrapped around the vagus nerve. The stimulator may be programmed in advance or may be activated on demand by placing a magnet against the generator implantation site.

While the mechanisms for the therapeutic effects of VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. An electrical stimulus is applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract.

Other types of implantable vagus nerve stimulators that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction are not addressed in this evidence review.

REGULATORY STATUS

Implantable VNS Devices

Several VNS therapy systems by Cyberonics Inc. have pre-market approval (PMA) from the U.S. Food and Drug Administration (FDA) for treatment of refractory partial-onset seizures and chronic or recurrent depression, when certain criteria are met. For example, in 1997, the

NeuroCybernetic Prosthesis (NCP®) system 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 VNS Therapy™ System was approved in 2005 “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.” FDA product code: LYJ

Non-implantable VNS Devices

Cerbomed has developed a transcutaneous VNS (t-VNS®) system, NEMOS®, that 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. Patients self-administer electric stimulation for several hours a day; no surgical procedure is required. The device has not been FDA approved for use in the US.

electroCore, LLC has developed a non-invasive VNS (gammaCore®) released for use by the FDA in April of 2017. The device is indicated for acute treatment of pain associated with episodic cluster and migraine headache in adults using noninvasive VNS on the side of the neck. Product code: PKR

EVIDENCE SUMMARY

VAGUS NERVE STIMULATORS

In order to assess the safety and effectiveness of vagus nerve stimulation (VNS), particularly for indications in which the primary outcomes are subjective (e.g., pain reduction, improved mood, improved functioning), well-designed, randomized controlled trials (RCTs) are necessary. Such trials include double-blinding, appropriate randomization, an appropriate control group (i.e., sham VNS or standard medical treatment), large study populations, adequate follow-up time, and adverse events reporting.

MEDICALLY REFRACTORY SEIZURES

The criteria for VNS for seizures are based on a 1998 BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) assessment[1], a 2015 Cochrane review[2] which included the five published double-blind randomized controlled trials (RCTs)[3-5], and numerous case series, retrospective reviews, and other non-randomized studies on adult[6-11], pediatric,[12-19] or mixed[20-25] patient populations. More recently, a 2020 Washington Health Care Authority Health Technology Assessment prepared by the Oregon Health and Science University Center for Evidence-based Policy was published on vagal nerve stimulation for the treatment of epilepsy and depression. All three reviews concluded that VNS reduced seizure frequency in patients with drug resistant partial-onset seizures.

The RCTs were large, well-designed multicenter trials that reported an approximate 25% reduction in partial-onset seizure frequency following three months of VNS. Adverse effects were mild and consisted primarily of hoarseness or voice change during “on” periods of stimulation. The remaining literature is limited to numerous non-randomized trials. Although evidence from non-randomized studies are generally considered unreliable for assessing the safety and effectiveness of VNS, the findings from these numerous studies have consistently shown significantly reduced seizure activity in patients with drug-resistant epilepsy. In addition,

clinical practice guidelines from the American Academy of Neurology stated that "…sufficient evidence exists to rank VNS for epilepsy as effective and safe…"[26] Thus, despite the lack of RCTs in the published clinical evidence, VNS has become a recognized standard of care for treatment in selected patients with medically refractory seizures.

REFRACTORY DEPRESSION

Technology Assessments

The 2020 Washington Health Care Authority Health Technology Assessment discussed above in relation to epilepsy also evaluated the effectiveness of VNS in the treatment of refractory depression.[27] Five studies met inclusion criteria, two of which are RCTs. The RCTs were rated to be at moderate risk of bias, one of the nonrandomized studies was at moderate risk of bias, and the two remaining nonrandomized studies had a high risk of bias. Comparators were low-stimulation VNS, sham VNS, and treatment as usual. Two of the RCTs and one of the nonrandomized studies reported on depression severity. No statistically significant differences were reported in the RCTs. In the nonrandomized study, the reported difference in reduction in depressive symptoms was significantly significant, with a greater reduction in the in the VNS plus treatment as usual group. One RCT each reported that high-stimulation VNS had higher rates of response than low-stimulation VNS and VNS and sham VNS had similar rates of response, and a nonrandomized study reported that VNS with TAU may be associated with higher rates of response than TAU alone. Across studies, no differences were reported in rates of suicide, except for one nonrandomized study that reported that VNS may be associated with higher rates of attempted suicide or self-inflicted injury (very-low-quality of evidence). Harms that were noted to be higher in VNS than sham VNS were voice alteration or hoarseness and cough.

A 2006 BCBSA TEC Assessment[28], evaluated the effectiveness of VNS in the treatment of refractory depression compared with continued medical management. The evidence consisted of one case series, one observational study, and one randomized controlled trial. The assessment found that "overall, the evidence supporting efficacy of VNS is not strong."

The randomized controlled trial (RCT) of 221 patients that compared VNS with a sham control (implanted but inactivated VNS) did not show a statistically significant difference between VNS and continued medical therapy in relieving depression symptoms.[29-31] The trial was short and possibly underpowered to detect a smaller amount of VNS benefit. In addition, the adequacy of blinding was questionable. The observational study included a subset of 205 VNS treated patients from the RCT described above who were followed long-term. A separately recruited control group of 124 patients received ongoing treatment for depression.[29, 32] Although the study findings favored the VNS therapy group, this evidence is considered unreliable due to significant methodological limitations including but not limited to the following: 1) Non-randomized allocation of treatment does not control for possible between-group differences in individual patient characteristics; thus, it cannot be ruled out that these differences, rather than the treatments received, were responsible for the observed outcomes; 2) The lack of a sham study group does not control for the expected placebo effects; 3) The inadequate, non-concurrent comparison group does not permit conclusions on the efficacy of VNS compared with placebo or other treatment options, 4) The differences in sites of care between VNS treated patients and controls may introduce response bias. (Analysis performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness.); and 5)

Differences in concomitant therapy changes cannot be ruled out as an explanation of the observed outcomes.

The case series (Study D-01) was a feasibility study of 60 patients receiving VNS; improvement was reported in depression scores.[33] It is uncertain whether loss to follow-up was addressed adequately in the analysis. In addition, the case series is limited by the lack of an appropriate comparison group.

Systematic Reviews

Bottomley (2020) reported results of a systematic review and meta-analysis of two RCTs (Rush [2005] and Aaronson [2013]), 16 single-arm studies, and four nonrandomized comparative studies of VNS for treatment-resistant depression.[34] The meta-analysis calculated overall pooled effect estimates for VNS and treatment-as-usual groups, respectively, but did not perform quantitative analysis of comparative treatment effects. There was statistically significant heterogeneity. Thus, this meta-analysis provides insufficient evidence to permit comparisons between VNS and the control groups.

In a meta-analysis that included 14 studies, Martin (2012) reported that among the uncontrolled studies in their analysis, 31.8% of subjects responded to VNS treatment.[35] However, results from a meta-regression to predict each study's effect size suggested that 84% of the observed variation across studies was explained by baseline depression severity ($p<0.0001$). The authors concluded that current data was insufficient to determine whether VNS is an effective treatment for depression and noted that positive results from uncontrolled studies may be due to placebo effect.

A 2008 systematic review and meta-analysis for VNS of treatment-resistant depression identified no new RCTs since the pivotal RCT described above, which the authors determined to be inconclusive.[36] As noted above, RCTs are considered the appropriate design for studying VNS for any indication. However, this review also included 17 nonrandomized, open studies which found VNS to be associated with a reduction in depressive symptoms. The authors concluded that, while open studies have reported promising results, further clinical trials are needed to study the mechanism of action and cost-effectiveness, and to confirm the efficacy of VNS in treatment-resistant depression.

Randomized Controlled Trials

No randomized controlled trials published after the search dates of the Washington Health Care Authority Health Technology Assessment were identified.

Nonrandomized Studies

Numerous non-randomized studies evaluated the effectiveness of VNS for the treatment of refractory depression.[33, 36-42] It is not possible to reach reliable conclusions from these studies as they fail to control for the biases discussed above.

TREATMENT OF CHRONIC HEART FAILURE

Systematic Reviews

Sant'Anna (2021) conducted a systematic review and meta-analysis on clinical trials comparing VNS with medical therapy for the management of chronic heart failure with reduced

ejection fraction.[43] Four RCTs and three prospective studies met inclusion criteria (n=1,263). Median follow-up was six months (range: 6 to 16 months). Only data from the RCTs were included in the meta-analysis. The certainty of the evidence based on GRADE characteristics was reported as high for all outcomes. The meta-analysis found significant improvements in New York Heart Association functional class, quality of life, six-minute walk test, and N-terminal-pro brain natriuretic peptide levels in patients treated with VNS compared to sham (Table 1). These studies are limited by a lack of long-term follow-up.

Table 1. Summary of systematic reviews.

Study	Improvement in NYHA functional class	Quality of Life	6-minute walk-test	NT-proBNP levels	Mortality
Sant'Anna (2021)[43]					
Total N	969 (4 RCTs)	450 (3 RCTs)	728 (3 RCTs)	445 (3 RCTs)	1206 (4 RCTs)
Pooled effect (95% CI)	OR, 2.72; (2.07 to 3.57); p<0.0001	MD, -14.18 (-18.09 to -10.28)	MD, 55.46 meters (39.11 to 71.81)	MD, -144.25 (-238.31 to -50.18)	OR, 1.24 (0.82 to 1.89)
I2 (p)	37% (p<0.0001)	49% (p<.0001)	0% (p<0.0001)	65% (p=0.003)	0% (p=0.43)

Randomized Controlled Trials

No RCTs have been published since the search dates of the above SR.

Nonrandomized Studies

In the ANTHEM-HF study (2014), 60 patients with heart failure with reduced ejection fraction were implanted with VNS, randomly assigned to right- or left-sided implantation (n=29 and 31, respectively), and followed for six months.[44] Overall, from baseline to six month follow-up, LV ejection fraction improved by 4.5% (95% confidence interval (CI) 2.4 to 6.6), left ventricular end systolic volume (LVESV) improved by -4.1 mL (95% CI -9.0 to 0.8), LVESD improved by -1.7 mm (95% CI -2.8 to -0.7), heart rate variability improved by 17 ms (95% Ci 6.5 to 28), and six-minute walk distance improved by 56 m (95% CI 37 to 75). Given there was no sham comparator group, it is unclear if the observed improvements may be attributed to VNS or some other confounding factor. A follow-up analysis to ANTHEM-HF by Nearing (2021) evaluated outcomes of VNS at 12, 24, and 36 months.[45] They found that LV ejection fraction improved by 18.7% (p=0.008), 19.3% (p=0.04), and 34.4% (p=0.009) at 12, 24, and 36 months, respectively, with high-intensity VNS. Individuals with low-intensity VNS only had significant improvement in LV ejection fraction at 24 months (12.3%; p=0.04). Although this data is promising, a lack of a no-VNS comparator group precludes drawing conclusions based on findings from the uncontrolled studies.

Several small case series describe VNS treatment outcomes in patients with heart failure; however, for the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.[46, 47]

TREATMENT OF UPPER-LIMB IMPAIRMENT DUE TO STROKE

Systematic Reviews

Gao (2023) examined VNS+Rehab for improving motor function, mental health and activities of daily living (ADL) postintervention and at the end of follow-up in patients with a stroke.[48]. Seven RCTs involving 263 (analyzed) participants was included. The effect size of VNS+Rehab over Rehab for motor function was medium postintervention (g=0.432; 95% CI 0.186 to 0.678) and large at the end of follow-up (g=0.840; 95% CI 0.288 to 1.392). No difference was found in the effect of VNS+Rehab over traditional rehabilitation for ADL, mental health or safety outcomes. The results suggest VNS+Rehab showed better motor function outcomes in patients after stroke, while no better than Rehab on mental health or ADL.

Ramos-Castaneda (2022) published a systematic review evaluating VNS on upper limb motor recovery after stroke.[49] Three RCTs by Dawson and Kimberley, which are summarized in the section below, were pooled for the analysis evaluating the role of implanted VNS. Results demonstrated that implanted VNS improved upper limb motor function based on Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score when compared to control (mean difference=2.78; 95% CI, 1.38 to 4.18).

Zhao (2022) published a systematic review and meta-analysis of RCTs evaluating vagus nerve stimulation in conjunction with rehabilitation therapies for restoring upper extremity function following stroke.[50] A total of five RCTs (n=178) met inclusion criteria. A significant effect of VNS compared to the control was identified for the primary outcome of Fugl-Meyer Assessment for Upper Extremity (FMA-UE, MD=3.59; 95% CI 2.55 to 4.63; p<0.01). No significant difference between groups in adverse events associated with the device was identified (RR=1.10; 95% CI 0.92 to 1.32; p=0.29).

Randomized Controlled Trials

Vagus Nerve Stimulation (VNS) paired with rehabilitation delivered by the Vivistim® Paired VNS™ System was approved by the FDA in 2021 to improve motor deficits in chronic ischemic stroke survivors with moderate to severe arm and hand impairment. Liu (2022) described the Vivistim implantation procedure, perioperative management, and complications for chronic stroke survivors enrolled in the pivotal trial.[51] The pivotal, multisite, randomized, triple-blind, sham-controlled trial (VNS-REHAB) enrolled 108 participants. All participants were implanted with the VNS device in an outpatient procedure. Thrombolytic agents were temporarily discontinued during the perioperative period. Participants were discharged within 48 hrs and started rehabilitation therapy approximately 10 days after the procedure. The rate of surgery-related adverse events was lower than previously reported for VNS implantation for epilepsy and depression. One participant had vocal cord paresis that eventually resolved. There were no serious adverse events related to device stimulation. Over 90% of participants were taking antiplatelet drugs (APD) or anticoagulants and no adverse events or serious adverse events were reported as a result of withholding these medications during the perioperative period. This study is the largest, randomized, controlled trial in which a VNS device was implanted in chronic stroke survivors.

Dawson (2021) conducted a randomized controlled trial of VNS in patients with upper limb dysfunction after ischemic stroke.[52] Patients with upper-limb dysfunction after ischemic stroke (n=106) were randomly assigned 1:1 to either VNS plus rehabilitation or rehabilitation with sham stimulation. The Fugl-Meyer Assessment-Upper Extremity score increased by 5 points in the VNS group and 2.4 points in the control group (between-group difference, 2.6; 95% CI 1.0 to 4.2; p=0.0014). Ninety days after in-clinic therapy, a clinically meaningful response was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the

control group (between-group difference, 24%; 95% CI, 6 to 41; p=0.0098). There was one adverse event of vocal cord paresis related to surgery in the control group.

A similar RCT with a smaller patient population was conducted by the same study group in 2016.[53] Twenty-one 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 and +3.0 in the control group (p=0.064). Six patients in the VNS group achieved a clinically meaningful response and four in the control group (p=0.17).

Kimberley (2018) reported results of a randomized, pilot sham-controlled RCT in 17 patients (VNS n=8 and sham VNS, n=9) with arm weakness after ischemic stroke.[54] The mean Fugl-Meyer assessment–upper extremity scores increased by 7.6 with VNS versus 5.3 points with sham at day one (Difference=2.3 points; 95% CI, −1.8 to 6.4; p=0.20) and 9.5 points with VNS versus 3.8 with sham at day 90 (Difference=5.7 points; 95% CI, −1.4 to 11.5; p=0.055). A Fugl-Meyer assessment–upper extremity score change of six points or greater was defined as response; the response rate at day 90 was 88% with VNS versus 33% with sham (p<0.05). There were three serious adverse events related to surgery: wound infection, shortness of breath and dysphagia, and hoarseness because of vocal cord palsy.

Longer-term follow-up studies are needed to evaluate long-term efficacy and safety.

TREATMENT OF TINNITUS

Systematic Review

Stegeman (2021) performed a systematic review of the treatment of tinnitus with vagus nerve stimulation.[55] A total of nine studies were identified, of which five examined transcutaneous VNS and four examined implanted VNS treatment. Two were RCTs, five were cohort studies, and two were case series. Six of the studies used a combined VNS/sound therapy treatment. All included studies had serious risk of bias. Due to heterogeneity in methodology, inclusion criteria, and assessed outcomes, no meta-analysis was completed. Most studies reported a small decrease in tinnitus distress or tinnitus symptom severity.

OTHER INDICATIONS

Nonrandomized Studies

Small case series (n≤40 patients) and one non-randomized comparison study described experiences with VNS in patients with bulimia, anxiety, Alzheimer's disease[56, 57], essential tremor[58], and eating disorders including obesity and food cravings[59]. The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited but there are no RCTs. For the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.

NONINVASIVE (TRANSCUTANEOUS) VAGUS NERVE STIMULATORS

Only RCTs and systematic reviews of RCTs will be discussed, as case series are inadequate to determine the effect of the technology.

REFRACTORY EPILEPSY

Wu (2020) reported results of a systematic review and meta-analysis of three RCTs (n=280, range n=60 to 144) of transcutaneous VNS for the treatment of drug-resistant epilepsy.[60] All treatment groups underwent a cymba conchae stimulus at a frequency of 20 to 30-Hz. The control groups received various kinds of sham stimulation at a frequency of 1 HZ, the same frequency stimulation as treatment but at the non-auricular vagus nerve area or no stimulation. Meta-analysis of all three included RCTs found that seizure frequency was significantly reduced with transcutaneous VNS (Mean Difference [MD]=-3.29; 95% CI -6.31 to -0.27). However, meta-analysis of the two RCTs that reported responder rates (undefined) did not find a significant difference between the transcutaneous VNS and control groups (n=238; Odds Ratio [OR]=1.47; 95% CI 0.54 to 4.02]. All three RCTs assessed quality of life using the Quality of Life in Epilepsy Inventory (QOLIE)-31 scale, but found no significant differences between treatment and control groups. Important limitations of the RCTs include imprecision, risk of confounding due to potentially imbalanced use of important nonprotocol interventions (i.e., concomitant antiepileptic drugs), and unacceptable flaws in outcome assessment (i.e., unspecified definition of response, between-group differences in measurement timing, lack of electroencephalography data).

PSYCHIATRIC DISORDERS

Li (2022) published results of an RCT comparing transcutaneous auricular VNS with citalopram for the treatment of major depressive disorder.[61] A total of 107 patients from the outpatient departments of three hospitals in China were randomly assigned to receive t-VNS or citalopram. Treatment was eight weeks of t-VNS, twice per day, plus a four-week follow-up or 12 weeks of citalopram. For the primary outcome of the 17-item Hamilton Depression Rating Scale (HAM-D17) measured every two weeks by trained interviewers blinded to the treatment assignment, although both groups improved significantly, there was no significant group-by-time interaction (95% CI -0.07 to 0.15, p=0.79). There was a significant difference between groups for remission rate at four and six weeks (p=0.007 and p=0.01, respectively), but not at any other time point.

Hein (2013) reported results of two pilot RCTs of a t-VNS device for the treatment of depression, one which included 22 subjects and the other with 15 subjects.[62] In the first study, 11 subjects each were randomized to active or sham t-VNS. At two weeks follow-up, Beck Depression Inventory (BDI) self-rating scores in the active-stimulation group decreased from 27.0 to 14.0 points (p<0.001), while the sham-stimulated patients did not show significant reductions in the BDI (31.0 to 25.8 points). In the second study, seven patients were randomized to active t-VNS and eight patients were randomized to sham t-VNS. In this study, BDI self-rating scores in the active stimulation group decreased from 29.4 to 17.4 points (p<0.05) after two weeks, while the sham-stimulated patients did not show significant change in BDI (28.6 to 25.4 points). The authors do not report direct comparisons in BDI change between the sham- and active-stimulation groups.

Hasan (2015) reported a randomized trial of t-VNS for the treatment of schizophrenia.[63] Twenty patients were assigned either to active t-VNS or to sham treatment for 12 weeks. There was no statistically significant difference in the improvement of schizophrenia status during the observation period.

Shiozawa (2014) conducted a systematic review of studies evaluating the evidence related to transcutaneous stimulation of the trigeminal or vagus nerve for psychiatric disorders.[64] They found four studies that addressed t-VNS for psychiatric disorders and included a total of 84

subjects. Three of the four studies evaluated physiologic parameters in healthy patients and one evaluated pharmaco-resistant epilepsy (Stefan, previously described[65]). The authors also include a fifth study in a data table, although not in their text or reference list (Hein, previously described[62]) Overall, the studies included were limited by small size and poor generalizability.

IMPAIRED GLUCOSE TOLERANCE

Huang (2014) reported results of a pilot RCT of a t-VNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance.[66] The study included 70 patients with impaired glucose tolerance who were randomized to active or sham t-VNS, along with 30 controls who received no t-VNS treatment. After 12 weeks of treatment, patients who received active t-VNS were reported to have significantly lower two-hour glucose tolerance test results than those who received sham t-VNS (7.5 mmol/L vs 8 mmol/L; p=0.004).

TREATMENT OF UPPER-LIMB IMPAIRMENT DUE TO STROKE

Wu (2020) reported results of a pilot randomized sham-controlled trial of 21 patients (nVNS=10 and sham nVNS, n=11) treated with nVNS for upper limb motor function impairment following subacute ischemic stroke.[67] The mean Fugl-Meyer assessment–upper extremity scores increased by 6.90 with nVNS versus 3.18 points with sham after 15 days of intervention (Difference= -3.72 points; 95% CI −5.12 to -2.32; p≤0.001). The improvement in the mean Fugl-Meyer assessment–upper extremity scores remained significantly higher at both the four-week (+7.70 vs. +3.36; p≤0.001) and the 12-week (+7.40 vs. +4.18; p=0.038) follow-ups. There was only one adverse event noted, which was that one patient in the nVNS group developed skin redness at an electrode point of contact.

PAIN

Natelson (2021) reported results of a small RCT with limited follow-up of nVNS for the treatment of pain and migraine in Gulf War Veterans with Gulf War Illness.[68] During the first 10 weeks, the 27 participants were randomized to receive active or sham nVNS, followed by 10 weeks of open-label trial. No significant differences between active and sham nVNS were identified.

Kutlu (2020) reported results of an RCT that compared a home-based exercise treatment program with or without auricular VNS in 60 female patients in Turkey with fibromyalgia syndrome (auricular VNS n=30 and no auricular VNS n=30).[69] The VNS was delivered at Beykoz Public Hospital's Department of Physical Therapy and Rehabilitation in 30-minute sessions on weekdays for four weeks. The home-based exercise program consisted of strengthening, stretching, isometric, and posture exercises that targeted the body and upper and lower extremities. When added to exercise, auricular VNS did not significantly improve mean scores on the Fibromyalgia Impact Questionnaire (37.27 vs. 41.93; p=0.378) or on any 36-Item Short Form Health Survey subscales (e.g., Physical Function: 80.00 vs. 85.00; p=.167). An important limitation of this RCT is the lack of a sham control group.

CLUSTER HEADACHE

Prevention of Cluster Headaches

Gaul (2016, 2017) reported the results of the PREVA study - a randomized open-label study of nVNS as a prophylactic therapy for chronic cluster headache (CH) in patients diagnosed at least one year prior to enrollment.[70, 71] The study was funded by the device manufacturer. In a

two-week baseline period, all 97 participants received only their individualized standard of care (SoC). Patients were then randomized to a four-week period of SoC with nVNS (n=48) or SoC alone, i.e., control (n=49). Four participants from the SoC with nVNS chose to withdraw; one control participant was removed from the study for failing to meet enrollment criteria. In an optional four-week period following, all participants received SoC with nVNS (n=92); 70 completed the optional period (11 controls discontinued from each group).

Efficacy was evaluated by the mean number of CH attacks per week, defined as the number of attacks during the last two weeks of the randomized phase minus the number of attacks during baseline divided by two. Safety and tolerability were assessed in those who were assigned treatment; and the intent-to-treat (ITT) population was those who had more than one efficacy recording in their home diary after randomization.

In the ITT population (n=45 SoC plus nVNS, n=48 in control) authors reported a mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI 0.5 to 7.2; p=0.02). However, the proportion of participants receiving SoC plus nVNS in the ITT population from the randomized phase with more than 50% response to treatment was 40.0, and in controls who went on to receive treatment in the extension phase, the proportion was 16.7.

During the randomization phase, 38% participants in the SoC plus nVNS group experienced adverse events (AEs), and 27% of controls experienced AEs. In the extension phase, 25% and 24% experienced AEs, respectively. Overall, the most common AEs for any treatment were CH attacks, headache, nasopharyngitis, dizziness, oropharyngeal pain, and neck pain. No serious AEs were considered related to the nVNS device.

The study is limited by a sham placebo control group, which may result in placebo response in the nVNS group. Additionally, the double-blind, study treatment period was less than one month, which limits inference about continued response.

Section Summary

Transcutaneous (or noninvasive) VNS has been investigated for preventing cluster headaches in one RCT. The PREVA study of prevention of cluster headache in patients with chronic cluster headache demonstrated a statistically significant increase in the proportion of patients with a 50% or greater reduction in the mean number of headache attacks and statistically significant reduction in the frequency of attacks for nVNS compared to standard of care with a treatment period of four weeks. There was also an improvement in quality of life as measured by the EQ-5D. However, the study was not blinded.

Treatment of Cluster Headaches

In 2016, Silberstein reported results from the manufacturer funded ACT1 study – a randomized, double-blind, sham-controlled study of nVNS as a treatment for cluster headache (CH).[72] One hundred fifty subjects were randomized to receive sham control or nVNS treatment for less than or equal to one month; completers could enter a three-month nVNS open-label phase. Limitations of this study include that the enrolled population was not reflective of relevant diversity (3.3% Asian, 8% Black, 87.3% white, 1.4% race/ethnicity not reported), a lack of quality of life or functional outcomes, and short follow-up time. In addition, a considerable proportion of patients correctly guessed their treatment allocation after their first treatment, though blinding was found to have improved by the end of the one-month period. The primary end point was response rate, defined as the proportion of subjects who achieved

pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. Secondary end points included the sustained response rate (15 to 60 minutes). Subanalyses of episodic cluster headache (eCH) and chronic cluster headache (cCH) cohorts were prespecified.

During the randomized phase of one month, 14 participants discontinued participation from the treatment group, and 8 in the control group discontinued. In the three-month open label period, 17 and 11 discontinued from the treatment and control groups, respectively. Application site reactions and nervous system AEs occurred more frequently with sham treatment than with nVNS in the double-blind phase. Adverse device effects (ADEs) were reported by 35/150 (nVNS, 11; sham, 24) subjects in the double-blind phase and 18/128 subjects in the open-label phase.

Intent-to-treat analysis included 133 subjects: 60 nVNS-treated (eCH, n=38; cCH, n=22) and 73 sham-treated (eCH, n=47; cCH, n=26). Authors reported a response in 26.7% of nVNS-treated subjects and 15.1% of sham-treated subjects. Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2%; sham,10.6%; *p*=0.008) but not the cCH cohort (nVNS, 13.6%; sham, 23.1%; *p*=0.48). Sustained response rates were significantly higher with nVNS for the eCH cohort and total population.

In 2018, Goadsby reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of acute cluster headache attacks.[73] Ninety-two patients with cluster headaches were randomized to nVNS or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the nVNS and sham treatment groups. The primary efficacy end point was the ability to achieve pain-free status within 15 minutes of initiation of treatment without use of rescue treatment. There was no difference between nVNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between nVNS-treated and sham-treated patients. For the episodic cluster headaches subgroup, nVNS demonstrated a 48% response rate compared with 6% response rate for sham-treated (p<0.01). The interaction p-value for the subgroup analysis was statistically significant (p=0.04).

de Coo (2019) combined the data from ACT1 and ACT2 meta-analytically for the two primary outcomes reported in the two studies.[74] The authors reported an interaction between treatment group and cluster headache subtype in the pooled analysis (p<0.05 for both outcomes).

Section Summary

The ACT1 and ACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. The RCTs reported slightly different outcome measures so that consistencies in magnitude of treatment effects cannot be assessed. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1 at 15 minutes into the first attack (27% vs. 15%, p=0.10) and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks (12% vs. 7%, p=0.33). However, in the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2 the proportion of attacks with a pain intensity score of 0 or 1 at 30 minutes was statistically significant overall (43% vs. 28%, p=0.05). The proportion of attacks that were pain-free at 15 minutes was similar in the two treatment groups

overall (14% vs. 12%) but a significant interaction was reported (p=0.04). There was a statistically significantly higher proportion of attacks in the episodic subgroup that were pain-free at 15 minutes in the nVNS group compared to sham (48% vs. 6%, p<0.01). Quality of life and functional outcomes have not been reported. Treatment periods ranged from only two weeks to one month with extended open-label follow-up of up to three months. Studies designed to test the effect of nVNS in the episodic subgroup with longer treatment and follow-up and including quality of life and functional outcomes are needed.

There are few adverse events of nVNS and they are mild and transient.

MIGRAINE

Prevention of Migraine Headaches

Diener (2019) published results of the PREMIUM trial, a phase 3, multicenter, sham-controlled RCT conducted in several European countries. Patients who experienced 5 to 12 migraine days per month were included.[75] The study began with a four-week run-in period during which no treatment was administered; 477 participants entered the run-in. The criteria to remain eligible after run-in were not described in the publication. After run-in, 341 participants were randomized (nVNS, n=169 or sham, n=172) to a 12-week double-blind treatment period followed by a 24-week open-label period of nVNS. Patients administered two 120-second stimulations bilaterally to the neck with gammaCore, three times daily. nVNS was not statistically significantly superior to sham with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last four weeks (32% vs 25%; p=0.19), reduction in number of migraine days from baseline to the last four weeks (-2.3 vs -1.8; p=0.15), or acute medication days (-1.9 vs -1.4; p=0.11) in the intention-to-treat population. Adverse events were reported in 44% of the nVNS group and 53% of the sham group. The PREMIUM II trial was a multicenter, sham-controlled RCT conducted in several U.S. sites and included patients who experienced 8 to 20 headache days per month with at least 5 of the days being migraine days.[76] The study included a 4-week run-in period during which no treatment was administered (N=336). After the run-in period, 231 patients were randomly assigned to receive nVNS (n = 114) or sham (n = 117) therapy during the double-blind period and were part of the intention to treat (ITT) population (ie, had ≥1 study treatment during the double-blind phase). The COVID-19 pandemic led to an early termination of this trial, therefore, the population was approximately 60% smaller than the statistical target for full power. The modified ITT (mITT) population, which included those who were at least 66% adherent to treatment during the double-blind phase, included 56 patients in the nVNS group and 57 in the sham group. Results showed that in the mITT population, nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12 (mean difference=-0.83 days; p=.2329), nor other outcomes such as mean change in the number of headache days or acute medication days. However, in the mITT population, the percentage of patients with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group (44.87%) than in the sham group (26.81%; p=.048). Furthermore, nVNS was significantly better than sham at decreasing headache impact, as measured by the Headache Impact Test-6 (HIT-6), and at decreasing migraine-related disability, as measured by the Migraine Disability Assessment Scale (MIDAS).

The EVENT trial (Silberstein, 2016) was a feasibility study of prevention with a sample size of 59.[77] It was not powered to detect differences in efficacy outcomes. About twenty percent of participants discontinued treatment after the first two months. The study was supposed to be

blinded, but the sham did not deliver electrical stimulation, which may have compromised the blinding. For the outcome of response, defined as 50% or more reduction in the number of headache days, 10% of the patients in the nVNS group versus 0% in the sham group were responders; statistically testing was not performed.

Section Summary

Three RCTs have evaluated nVNS for prevention of migraine. The EVENT trial was a feasibility study of prevention of migraine that was not powered to detect differences in efficacy outcomes. It does not demonstrate the efficacy of nVNS for prevention of migraine. The PREMIUM trial was a phase 3, multicenter, sham-controlled RCT including 341 randomized participants with a 12-week double-blind treatment period. The results of PREMIUM demonstrated that nVNS was not statistically significantly superior to sham. With respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last four weeks, reduction in number of migraine days from baseline to the last four weeks or acute medication days. The PREMIUM II trial was a multicenter, sham-controlled RCT including 231 randomized participants with a 12-week double-blind treatment period. Results demonstrated that treatment with nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12, nor other outcomes such as mean change in the number of headache days or acute medication days. However, the percentage of participants with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group than in the sham group. However, interpretation of these findings is limited as it was based on a mITT population of 49% of randomized patients (n= 113 of original 231 participants) due to COVID-19 pandemic-related early termination.

Treatment of Migraine Headaches

The Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS) for the Acute Treatment of Migraine (PRESTO) trial was a multicenter, double-blind, randomized, sham-controlled trial of acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura reported by Tassorelli (2018), Grazzi (2018), and Martelletti (2018).[78-80] The primary efficacy outcome was the proportion of participants who were pain-free without using rescue medication at 120 minutes. There was not a statistically significant difference in the primary outcome (30% vs 20%; p=0.07) although it favored the nVNS group. The nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs 18%; p=0.02). PRESTO results did not include quality of life or functional outcomes and the double-blind treatment and follow-up period was 4 weeks. In the additional four weeks of acute nVNS in the open-label period, rates of pain-free response after the first treated attack (28%,) and pain relief (43.4%) were similar to the rates in the double-blind period. Given the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed.

Section Summary

One RCT has evaluated nVNS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs. 20%; p = 0.07). However, the nVNS group had a higher

proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs. 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs. 18%; p=0.02). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind treatment period was four weeks with an additional four weeks of open-label treatment. Given the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed.

OTHER INDICATIONS

Small studies of transcutaneous VNS have also been reported for gastrointestinal dysfunction in Parkinson's disease[81], systemic lupus erythematosus[82], cortical arousal and alertness[83], and delayed neurocognitive recovery in elderly patients.[84] Larger studies are needed to know how well transcutaneous VNS works in these populations.

ADVERSE EVENTS

The most commonly reported adverse effects of VNS have been mild and consist primarily of hoarseness of voice during "on" periods of stimulation, transient throat pain, and coughing. More serious adverse events reported include, but are not limited to direct delivery of the current to the nerve due to generator malfunction; modified synchronization between cardiac and respiratory activity affecting the oxygen delivery to tissues; heart block with ventricular standstill; bradyarrhythmias and severe asystolia; and changes in respiration during sleep.[1, 29, 36, 85-88]

PRACTICE GUIDELINE SUMMARY

AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association (APA) (2010, reaffirmed 2015) has level III* recommendations regarding the use of vagus nerve stimulation (VNS) for patients with major depressive disorder.[89] Strategies to address nonresponse during an acute phase of depression include VNS as an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT (electroconvulsive therapy). Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality.

* [III] May be recommended on the basis of individual circumstances (As opposed to level I or II which are recommended with substantial and moderate clinical confidence, respectively.)

AMERICAN ACADEMY OF NEUROLOGY

The American Academy of Neurology (AAN) 2013 consensus statement (reaffirmed in 2016 and 2019) states VNS may be considered for seizures in children, for LGS (Lennox-Gastaut-syndrome)- associated seizures, and for improving mood in adults with epilepsy; and VNS may be considered to have improved efficacy over time.[90] These statements are based on Level C evidence, which is defined as, "possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population."

DEPARTMENT OF VETERANS AFFAIRS AND THE DEPARTMENT OF DEFENSE

A 2020 clinical practice guideline from the Department of Veterans Affairs and the Department of Defense (VA/DoD) addressed the primary care management of headache. The guideline included a recommendation with a weak strength of evidence which stated, “We suggest non-invasive vagus nerve stimulation for the acute treatment of episodic cluster headache.”

SUMMARY

Vagus nerve stimulation (VNS) has evolved to be a standard of care as a treatment of medically refractory seizures. Therefore, VNS for medically refractory seizures may be considered medically necessary for patients who have had inadequate response to or are intolerant of at least two antiepileptic drugs.

In certain situations, a stimulator may require revision after it has been placed. In these cases, revision may be medically appropriate to allow for the proper functioning of the device. Therefore, revision(s) to an existing stimulator may be considered medically necessary after the device has been placed.

In certain situations, a stimulator may no longer be able to perform its basic function due to damage or wear. When a stimulator is out of its warranty period and cannot be repaired adequately to meet the patient’s medical needs, replacement of the device may be medically appropriate. Therefore, replacement of all or part of a stimulator may be considered medically necessary when device replacement Criteria are met.

When a stimulator is in its warranty period or can be repaired or adapted adequately to meet the patient’s medical needs, replacement of the device is considered not medically necessary.

There is not enough research to make conclusions about the benefit of VNS as a treatment for conditions other than medically refractory seizures. Therefore, VNS is considered investigational for all indications other than selected patients with refractory seizures.

There is not enough research to know if or how well transcutaneous and non-implantable vagus nerve stimulators (nVNS) work to treat people with any condition, including but not limited to cluster headache. This does not mean that they do not work, but more research is needed to know. No clinical guidelines based on research recommend these stimulators for people with cluster headache or any other condition. Therefore, transcutaneous and non-implantable vagus nerve stimulators are considered investigational as a treatment for all indications.

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CODES

Codes	Number	Description
CPT	61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
	61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
	64568	Open implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
	64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
	64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	95970	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 brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	95971	;with simple spinal cord, or peripheral nerve (eg, sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
	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,

Codes	Number	Description
		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	;with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
HCPCS	C1827	Generator, neurostimulator (implantable), non-rechargeable, with implantable stimulation lead and external paired stimulation controller
	E0735	Non-invasive vagus nerve stimulator
	~~K1020~~	~~Non-invasive vagus nerve stimulator~~ (Deleted 01/01/2024)
	L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month
	L8679	Implantable neurostimulator, pulse generator, any type
	L8680	Implantable neurostimulator electrode, each
	L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
	L8682	Implantable neurostimulator radiofrequency receiver
	L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
	L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
	L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

Date of Origin: *February 1998*