Vagus Nerve Stimulation

Policy #: 00134
Original Effective Date: 06/05/2002
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider vagus nerve stimulation (VNS) as a treatment of medically refractory seizures to be eligible for coverage.

Note: Medically refractory seizures are defined as seizures that occur in spite of therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse effects of these drugs.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of vagus nerve stimulation (VNS) as a treatment in patients with seizures other than medically refractory seizures to be investigational.*

Based on review of available data, the Company considers vagus nerve stimulation (VNS) as a treatment for any other condition, including but not limited to heart failure, fibromyalgia, depression, essential tremor, obesity, headaches, tinnitus, and traumatic brain injury to be investigational.*

Based on review of available data, the Company considers non implantable vagus nerve stimulation (VNS) devices for all indications to be investigational.*

Background/Overview

Vagus Nerve Stimulation
VNS was initially investigated as a treatment alternative in patients with medically refractory partial-onset seizures for whom surgery is not recommended or for whom surgery has failed. Over time, the use of VNS has expanded to generalized seizures, and it has been investigated for a range of other conditions.

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. 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. There are also vagal efferent pathways that

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innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract that may also be stimulated by VNS.

The type of VNS device addressed in this policy consists of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping 2 spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular times or on demand by patients or family by placing a magnet against the subclavicular implant site.

Other types of VNS are also available. The Maestro® System (EnteroMedics, St. Paul, MN) consists of a subcutaneously-implanted pulse generator and electrodes that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction. These types of stimulators differ in the location of the pulse generator and electrodes and the stimulation programming settings, and are not addressed in this policy.

Potential Indications for VNS

VNS was originally approved for the treatment of medically refractory epilepsy. Significant advances have occurred in surgical treatment for epilepsy and in medical treatment of epilepsy with newly developed and approved medications. Despite these advances, however, 25% to 50% of patients with epilepsy experience breakthrough seizures or suffer from debilitating adverse effects of antiepileptic drugs. VNS has been used as an alternative to or adjunct to epilepsy surgery or medications as a therapy for refractory seizures.

Based on observations that patients treated with VNS experienced improvements in mood, VNS has been evaluated for the treatment of refractory depression. VNS has been investigated for multiple other conditions which may be affected by either the afferent or efferent stimulation of the vagus nerve, including headaches, tremor, obesity, heart failure, fibromyalgia, tinnitus, and traumatic brain injury.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 1997, FDA approved a VNS device called the NeuroCybernetic Prosthesis (NCP®) system 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.”

Since 1997, it has been reported that recipients of a vagus nerve stimulator have experienced improvements in mood. Therefore, there has been research interest in VNS as a treatment for refractory depression. On July 15, 2005, Cyberonics received PMA supplement approval by FDA 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.”
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VNS therapy has also been investigated for use in other conditions such as headaches, obesity, and essential tremors. FDA product code: LYJ.

Cerbomed has developed a transcutaneous VNS (t-VNS\textsuperscript{®})\textsuperscript{‡} system 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 received the CE mark in Europe in 2011, but has not been FDA approved for use in the United States. Electrocore has developed a noninvasive VNS (gammaCore\textsuperscript{®})\textsuperscript{‡} that is currently being investigated for headache; the device does not have FDA approval.

Centers for Medicare and Medicaid Services (CMS)
Medicare has a national coverage determination for VNS. Medicare coverage policy notes that “Clinical evidence has shown that vagus nerve stimulation is safe and effective treatment for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. Vagus nerve stimulation is not covered for patients with other types of seizure disorders that are medically refractory and for whom surgery is not recommended or for whom surgery has failed.” Effective for services performed on or after May 4, 2007, VNS is not reasonable and necessary for resistant depression.

Rationale/Source
The review of evidence in this section will pertain to implantable vagus nerve stimulators unless otherwise indicated. The evidence on nonimplantable vagus nerve stimulators will be discussed separately.

Treatment of Seizures
Vagus Nerve Stimulation for Adult Partial-Onset Seizures
The policy regarding treatment of seizures has expanded the indications over time but was originally based, in part, on a 1998 TEC Assessment that offered the following conclusions.

- Published evidence from 2 large, well-designed multicenter randomized trials involving over 300 patients demonstrates that the use of VNS as an adjunct to optimal use of antiepileptic drugs in the treatment of medically refractory patients with at least 6 partial-onset seizures/month reduces seizure frequency by approximately 25% after 3 months of treatment. In patients who achieve an initial reduction in seizure frequency, the beneficial treatment effect appears to be maintained and may increase with time.
- Adverse effects are mild and consist primarily of hoarseness or voice change during “on” periods of stimulation.
- There is limited information about the use of VNS in patients with other types of seizure disorders.

Based on this TEC Assessment, earlier versions of this policy supported the use of VNS for partial-onset seizures for patients older than 12 years of age. A randomized controlled trial (RCT) published in 2014 reported long-term quality of life outcomes for 112 patients with pharmaco-resistant focal seizures, which supported the beneficial effects of VNS for this group.
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VNS for Adult Generalized Seizures
Tecoma and Iragui observed in a 2006 review that, since approval of VNS for partial seizures, a number of case series including patients with generalized seizures have been published. These series report seizure reduction rates similar to or greater than those reported in partial epilepsy and note that “this body of evidence suggests that VNS has broad antiepileptic efficacy.” The authors suggest that these results may be particularly important because resective epilepsy surgery is generally not feasible in these patients.

Other reports published since the Tecoma and Iragui review are consistent with the authors’ observations. In a French study of 50 consecutive refractory adolescents and adults who were not eligible for surgery and 11 of whom had generalized epilepsy, 58% were classified as responders at 3 year follow-up. Generalized epilepsy was predictive of a better outcome than partial epilepsy seizures. Seizure reduction of 61% was also reported in a case series of 12 patients with drug-resistant idiopathic generalized epilepsy. Garcia-Navarrete et al evaluated outcomes after 18 months of follow-up for a prospectively followed cohort of 42 patients with medication-resistant epilepsy who underwent VNS implantation. Subjects' seizure types were heterogeneous, but 52% had generalized epilepsy. Pharmacotherapy was unchanged during the course of the study. Twenty-seven subjects (63%) were described as "responders," defined as having a 50% or greater reduction in seizure frequency compared with the year before VNS implantation. The reduction in seizure frequency was not statistically significantly different between subjects with generalized and focal epilepsy.

VNS for Childhood Seizures
Since publication of the 1998 TEC assessment, there has been interest in expanding the use of VNS to younger patients. Several studies have now reported results that support the safety and efficacy of the device in children with refractory seizures. For example, 60 pediatric patients were treated as part of the double-blind clinical trials conducted to support the U.S. FDA application. At 18 months, the median reduction in seizure frequency was 50%, similar to the results achieved in adults. Adverse events were also similar to those recently reported in adults, and none resulted in termination of stimulation. Hornig et al reported on a case series of 19 pediatric patients, with observation periods ranging up to 30 months. Overall, 50% of patients had a 50% reduction in seizure frequency. Patwardhan et al reported that among 38 patients aged 11 months to 16 years with medically refractory seizures, both generalized and partial-onset, 29% had a greater than 90% reduction in seizure frequency after VNS implantation, while 39% had 50% to 90% reduction. Healy et al reported that among 16 patients younger than 12 years who underwent VNS implantation at a single center, 9 (56%) experienced a reduction in their seizure frequency of 50% or more. Results from an add-on study to an RCT designed to compare high-output with low-output VNS stimulation among 41 children with medically refractory epilepsy suggest that VNS does not have adverse effects on cognitive or psychosocial outcomes. Other studies of pediatric patients that included patients with generalized and partial-onset seizures have supported the use of VNS in reducing seizure frequency. These have included a series of 41 children treated with VNS, randomized to a high- or low-dose stimulation protocol, a retrospective case-control study with 36 VNS patients compared with 72 age- and sex-matched controls with refractory epilepsy not treated with VNS, a retrospective cohort study including 252 pediatric patients with a variety of seizure types treated with VNS, and a retrospective cohort study of 347 children with a variety of seizure types followed for up to 2 years postimplantation.
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Similar to adult studies, pediatric studies suggest that VNS improves seizure frequency in generalized epilepsy syndromes. In a multicenter study of 28 children with refractory seizures, You et al reported that 15 children (53.6%) showed a greater than 50% reduction in seizure frequency and 9 (32%) had a greater than 75% reduction, and there were no significant differences when groups were compared by seizure type or etiology. Tecoma and Iragui cite a multicenter retrospective analysis of 50 children with Lennox Gastaut syndrome (LGS) treated with VNS. Median seizure reduction at 6 months was 88% for tonic seizures and 81% for atypical absence. You et al compared VNS and total corpus callosotomy for LGS. Of the 14 patients who underwent a corpus callosotomy, 9 (64%) had a greater than 50% reduction in seizure frequency and 5 (36%) had a greater than 75% reduction. Of the 10 patients who underwent VNS implantation, 7 (70%) had a greater than 50% reduction in seizure frequency and 2 (20%) had a greater than 75% reduction. For 24 children with LGS or LGS-like syndrome who underwent VNS implantation, Cukiert et al reported that at least a 50% seizure frequency decrease was seen for 35 different seizure types.

The major limitations of VNS are the following issues: stimulation generally does not completely eliminate seizures, and it is not possible to predict which patients will optimally respond. One meta-analysis that included 74 retrospective and prospective studies assessing VNS efficacy in seizures found that predictors of efficacy included generalized epilepsy or mixed seizure types (compared with partial-onset seizures) and age younger than 18 years. In 2013, Arya et al reported results of a single-center retrospective chart review that included 43 pediatric patients who underwent VNS implantation over a 5-year period; the authors found that absence of magnetic resonance imaging lesion predicted a good outcome. These studies support the use of VNS in children, in patients with generalized epilepsy, and in those who are not candidates for surgery (ie, no identified structural brain abnormality).

Section Summary
The evidence on the efficacy of VNS for treatment of refractory seizures consists of 2 RCTs and numerous uncontrolled studies. The RCTs both reported a significant reduction in seizure frequency for patients with partial-onset seizures. The uncontrolled studies have consistently reported large reductions for a broader range of seizure types in both adults and children. The large reduction in seizures includes substantial numbers of patients who achieve a greater than 50% reduction in seizure frequency.

Treatment of Refractory Depression
Interest in the application of VNS for treatment of refractory depression is related to reports of improvement in depressed mood among epileptic patients undergoing VNS. TEC Assessments written in 2005 and updated in 2006 concluded that evidence was insufficient to permit conclusions of the effect of VNS therapy on health outcomes. The available evidence for these TEC Assessments included study groups assembled by the manufacturer of the device (Cyberonics) and have since been reported on in various publications. Analyses from these study groups were presented for FDA review and consisted of a case series of 60 patients receiving VNS (Study D-01), a short-term (ie, 3-month) sham-controlled RCT of 221 patients (Study D-02), and an observational study comparing 205 patients on VNS therapy with 124 patients receiving ongoing treatment for depression (Study D-04). Patients who responded to sham treatment in the short-term RCT (~10%) were excluded from the long-term observational study.
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The primary outcome evaluated was the relief of depression symptoms that can usually be assessed by any one of many different depression symptom rating scales. A 50% reduction from baseline score is considered to be a reasonable measure of treatment response. An improvement in depression symptoms may allow reduction of pharmacologic therapy for depression, with a reduction in adverse effects related to that form of treatment. In the studies evaluating VNS therapy, the 4 most common instruments used were the Hamilton Rating Scale for Depression, Clinical Global Impression, Montgomery and Asberg Depression Rating Scale, and the Inventory of Depressive Symptomatology (IDS).

Several case series studies published before the randomized trial showed 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, but there are some losses to follow-up. Natural history, placebo effects, and patient and provider expectations make it difficult to infer efficacy from case series data.

The randomized study (D-02) that compared VNS therapy with a sham control (implanted but inactivated VNS) showed a nonstatistically significant result for the principal outcome. Fifteen percent of VNS subjects responded versus 10% of control subjects (p=0.31). The Inventory for Depressive Symptomatology Systems Review (IDS-SR) score was considered a secondary outcome and showed a difference in outcome that was statistically significant in favor of VNS (17.4% vs 7.5%, respectively, p=0.04).

The observational study that compared patients participating in the RCT and a separately recruited control group (D-04 vs D-02, respectively) evaluated VNS therapy out to 1 year and showed a statistically significant difference in the rate of change of depression score. However, issues such as unmeasured differences between patients, nonconcurrent controls, differences in sites of care between VNS therapy patients and controls, and differences on concomitant therapy changes raise concern about this observational study. Analyses 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 of VNS and almost no statistically significant differences. Patient selection for the randomized trial and the observational comparison trial may be of concern. VNS is intended for treatment-refractory depression, but the entry criteria of failure of 2 drugs and a 6-week trial of therapy may not be a strict enough definition of treatment resistance. Treatment-refractory depression should be defined by thorough psychiatric evaluation and comprehensive management. It is important to note that patients with clinically significant suicide risk were excluded from all VNS studies. Given these concerns about the quality of the observational data, these results did not provide strong evidence for the effectiveness of VNS therapy.

In addition to the results of the TEC Assessment, several systematic reviews and meta-analyses have addressed the role of VNS in treatment resistant depression. A systematic review of the literature for VNS of treatment-resistant depression identified the randomized trial previously described among the 18 studies that met the study’s inclusion criteria. VNS was found to be associated with a reduction in depressive symptoms in the open studies. However, results from the only double-blind trial were considered to be inconclusive. Daban et al concluded that further clinical trials are needed to confirm efficacy of VNS in treatment-resistant depression.
In a meta-analysis that included 14 studies, Martin and Martin-Sanchez reported that among the uncontrolled studies in their analysis, 31.8% of subjects responded to VNS treatment. 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. Berry et al reported results from a meta-analysis of 6 industry-sponsored studies of safety and efficacy for VNS in treatment-resistant depression, which included the D-01, D-02, Bajbouj et al (D-03), D-04, and Aaronson et al (D-21) study results. In addition, the meta-analysis used data from a registry of patients with treatment-resistant depression (335 patients receiving VNS and treatment as usual and 301 patients receiving treatment as usual) that were unpublished at the time of the meta-analysis publication (ClinicalTrials.gov identifier: NCT00320372). The authors report that adjunctive VNS was associated with a greater likelihood of treatment response (odds ratio, 3.19; 95% confidence interval [CI], 2.12 to 4.66). However, the meta-analysis did not have systematic study selection criteria, limiting the conclusions that can be drawn from it.

In 2014, Liu et al conducted a systematic review of brain stimulation treatments, including deep brain stimulation, electroconvulsive therapy, transcranial magnetic stimulation, and VNS, for mental illnesses other than nonpsychotic unipolar depression in adults 65 years or older. The authors identified 2 small studies which evaluated the effect of VNS on cognition in patients with Alzheimer disease, 1 with 10 subjects and 1 with 17 subjects, which were mixed in demonstrating clinical improvements.

In 2013, Aaronson et al reported results from an active-controlled trial in which 331 patients with a history of chronic or recurrent bipolar disorder or major depressive disorder, with a current diagnosis of a major depressive episode, were randomized to 1 of 3 VNS current doses (high, medium, low). Patients had a history of failure to respond to at least 4 adequate dose/duration of antidepressant treatment trials from at least 2 different treatment categories. After 22 weeks, the current 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 the dose groups for the study's primary outcome, change in IDS score from baseline. However, the mean IDS score improved significantly for each of the groups from baseline to the 22-week follow-up. At 50 weeks of follow-up, there were no significant differences between the treatment dose groups for any of the depression scores used. Most patients 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%. Interpretation of the IDS improvement over time is limited by the lack of a no treatment control group. Approximately 20% of the patients included had a history of bipolar disorder; as such, the results may not be representative of most patients with treatment resistant unipolar depression.

Other case series do not substantially strengthen the evidence supporting VNS. A case series study by Bajbouj et al that followed patients for 2 years showed that 53.1% (26/49) patients met criteria for a treatment response and 38.9% (19/49) met criteria for remission. A small study of 9 patients with rapid-cycling bipolar disorder showed improvements in several depression rating scales over 40 weeks of observation. Another case series by Cristancho et al that followed patients for 1 year showed that 4 of 15 responded and 1 of 15 remitted according to the principal response criteria. In a 2014 case series which included 27 patients with treatment resistant depression, 5 patients demonstrated complete remission after 1 year and 6 patients were considered responders.
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Adverse effects of VNS therapy included voice alteration, headache, neck pain, and cough, which are known from prior experience with VNS therapy for seizures. Regarding specific concerns for depressed patients such as mania, hypomania, suicide, and worsening depression, there does not appear to be a greater risk of these events during VNS therapy.

Section Summary
There is 1 RCT evaluating the efficacy of VNS for resistant depression. This study reported only short-term results and found no significant improvement for the primary outcome with VNS. Other available studies, which include nonrandomized comparative studies and case series, are limited by relatively small sizes and the potential for bias in selection; the case series are further limited by the lack of a control group. Given the limitations of this literature, combined with the lack of substantial new clinical trials, the scientific evidence is considered to be insufficient to permit conclusions concerning the effect of this technology on major depression.

Other Conditions
Treatment of Essential Tremor
Handforth et al studied VNS in 9 patients with essential tremor. Four weeks after implantation of the VNS device, tremor assessment using a masked videotape of patients was performed. Raters found no improvement in upper-extremity tremors. Therefore, the authors of the study concluded that VNS is not likely to have any clinically meaningful effect in essential tremor treatment.

Treatment of Headaches
Drawing on the analgesic effects noted with VNS in the treatment of depression, Mauskop evaluated VNS in 5 patients with severe, refractory chronic cluster and migraine headaches. Mauskop reported excellent results in 1 patient who was able to return to work and significant improvement in 2 patients. Other than nausea developed by 1 patient, VNS was well-tolerated. Cecchini et al evaluated VNS in 4 patients suffering from daily headache and chronic migraine. However, these studies are too small to draw conclusions on the effects of VNS for the treatment of headache, and further study is needed.

Treatment of Obesity
Unintended weight loss has been observed in participants in studies of VNS, prompting interest in use of the technology to prevent or treat obesity. Bodenlos et al investigated whether VNS might affect food cravings in patients with chronic, treatment-resistant depression. They recruited 33 participants and divided them into 3 groups: 11 subjects receiving VNS for depression, 11 patients with depression but not receiving VNS, and 11 healthy controls. Most participants (42%) had a body mass index (BMI) in the normal range. Participants viewed food images on a computer in random order and then a second time in the same order and were asked after each viewing how much they would like to eat each food if it were available and how well they would be able to resist tasting each one. VNS devices were turned on for one viewing and off for the other. The depression VNS group had greater differences in food cravings between viewings in the sweet food category than the other 2 groups. No significant differences between groups were found for foods in proteins and vegetables/fruit categories. A significant proportion of the variability in VNS-related changes in cravings for sweet foods was attributed to clinical VNS device settings, depression scores, and BMI. A number of limitations in the study prevent drawing conclusions about the impact of VNS on eating.
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Behavior including small study size, selection and lack of randomization, heterogeneity of groups with respect to depression, BMI, and age. Comorbidities including anxiety and medical conditions and drugs that might influence food intake and cravings were not considered. Large, well-designed and executed controlled studies are needed to evaluate the impact of VNS on eating behavior and obesity.

Treatment of Chronic Heart Failure
In 2014, Zannand et al reported results from the NECTAR-HF trial, a randomized, sham-controlled trial, with outcomes from VNS in patients with severe left ventricular (LV) dysfunction, despite optimal medical therapy. Ninety-six patients were implanted with VNS and randomized in a 2:1 manner 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 end point data collection were blinded to randomization. Sixty-three patients were randomized to the intervention, of whom 59 had paired pre-post data available, while 32 were randomized to control, of whom 28 had paired data available. The analysis was a modified intention-to-treat. For the primary end point of change in left ventricular end systolic diameter (LVESD) from baseline to 6 months, there were no significant differences between groups (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 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 vs from 37.7 to 38.4 in the control group; p=0.02). Subject blinding was found to be imperfect, which may have biased the subjective outcome data reporting.

In the ANTHEM-HF study, 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 6 months. Overall, from baseline to 6-month follow-up, LV ejection fraction improved by 4.5% (95% 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 6-minute walk distance improved by 56 m (95% CI, 37 to 75). A case series phase 2 trial of VNS therapy for chronic heart failure was published previously, which reported improvements in New York Heart Association class quality of life, 6-minute walk test, and LV ejection fraction.

Treatment of Fibromyalgia
Lange et al conducted a phase 1/2 trial of VNS of 14 patients with fibromyalgia. At 3 months, 5 patients had attained efficacy criteria based on a composite measure of improvement of fibromyalgia symptoms. At 11 months, 8 patients met efficacy criteria. This single-arm trial does not provide sufficient evidence for efficacy of VNS for this indication.

Treatment of Tinnitus
A 10-patient case series by De Ridder et al suggested that VNS may be associated with clinical improvements in patients with tinnitus.
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Treatment of Traumatic Brain Injury
Shi et al have FDA approval to conduct a small pilot study to evaluate VNS in the treatment of traumatic brain injury.

Nonimplantable VNSs
Transcutaneous VNS for Epilepsy
Aihua et al reported results from a series of 60 patients with pharmacoresistant epilepsy treated with a transcutaneous VNS (t-VNS) device, who were randomly assigned to receive 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. Thirty patients were randomized to each group; 4 subjects from the treatment group were excluded from analysis due to loss to follow-up (n=3) or adverse effects (n=1), while 9 subjects from the control group were excluded from analysis due to loss to follow-up (n=2) or increase or lack of decrease in seizures or other reasons (n=7). In the treatment group, compared with baseline, the median monthly seizure frequency was significantly reduced after 6 months (5.5 vs 6.0; p<0.001) and 12 months (4.0 vs 6.0; p<0.001) of t-VNS therapy. At 12-month follow-up, t-VNS group subjects had a significantly lower median monthly seizure frequency compared with the control group (4.0 vs 8.0; p<0.001).

Two small case series were identified that used a transcutaneous stimulator (t-VNS device) for treatment of medication refractory seizures. In a small case series of 10 patients with treatment resistant epilepsy, Stefan et al reported that 3 patients withdrew from the study, while 5 of 7 patients reported a reduction in seizure frequency. In another small case series, He et al reported that among 14 pediatric patients with intractable epilepsy who were treated with bilateral t-VNS stimulation, of the 13 patients who completed follow-up, mean reduction in self-reported seizure frequency was 31.8% after 8 weeks, 54.1% from week 9 to 16, and 54.2% from week 17 to 24.

Transcutaneous VNS for Psychiatric Disorders
Hein et al reported results of 2 pilot RCTs of a t-VNS device for the treatment of depression, one which included 22 subjects and one with 15 subjects. In the first study, 11 subjects each were randomized to active or sham t-VNS. At 2 weeks follow-up, Beck Depression Inventory (BDI) self-rating scores in the active-stimulation group decreased from 27.0 to 14.0 (p< 0.000), while the sham-stimulated patients did not show significant reductions in the BDI (31.0–25.8 points). In the second study, 7 patients were randomized to active t-VNS and 8 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 (p<0.05) after 2 weeks, while the sham-stimulated patients did not show significant change in BDI (28.6 to 25.4). The authors do not report direct comparisons in BDI change between the sham- and active-stimulation groups.

Shiozawa et al conducted a systematic review of studies evaluating the evidence related to transcutaneous trigeminal or VNS for psychiatric disorders. In the article text, the authors state that they reviewed studies, 4 of which addressed t-VNS for psychiatric disorders and included a total of 84 subjects. Of those 4, 3 of the studies evaluated physiologic parameters in healthy patients, and 1 evaluated pharmacoresistant epilepsy (Stefan et al, previously described). The authors also include a fifth study in 1 data table, although not in
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their text or reference list (Hein et al, previously described) Overall, the studies included were limited by small size and poor generalizability.

Transcutaneous VNS for Other Disorders
Goadsby et al reported results from an open-label pilot study of t-VNS for the treatment of migraine with or without aura. Eighty migraine attacks were self-treated by 27 patients, of an initial sample of 30 patients (2 patients treated no migraine attacks with the device, 1 patient treated only an aura). Of 54 moderate or severe attacks treated, 12 subjects (22%) were pain-free at 2 hours posttreatment. Thirteen subjects reported adverse events, which were all considered mild or moderate.

Kreuzer et al reported a single-armed pilot study of t-VNS with 2 different devices for the treatment of tinnitus. Forty-eight subjects were included in the study's primary intention-to-treat analysis. For the study's primary outcome of change in mean Tinnitus Questionnaire (TQ) score from baseline to 6-month follow-up, for the 24 subjects in the first phase of the study, who had used an earlier generation t-VNS device (Cerbomed), the TQ total score decreased by 3.7 points (p=0.036). Nine subjects (37.5%) were considered responders. For the 24 subjects in the second phase of the study, who had used a later-generation t-VNS device (Cerbomed), the mean TQ score decreased by 2.8 points (p=0.014). Eleven subjects were considered responders (45.8%). In a per-protocol analysis, which included 28 subjects who received treatment, there was no significant improvement in TQ scores. The authors conclude that t-VNS treatment did not result in significant improvement in tinnitus.

Huang et al reported results of a pilot RCT of a t-VNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance. 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 2-hour glucose tolerance test results than those who received sham t-VNS (7.5 vs 8 mmol/L; p=0.004).

Section Summary
Transcutaneous VNS has been investigated for a number of conditions. Some evidence for the efficacy of t-VNS for epilepsy comes 1 small RCT, which reported lower seizure rates for active t-VNS-treated patients compared with sham controls; however, the high dropout rates in this study limit conclusions that may be drawn. One small RCT which compared t-VNS with sham stimulation for the treatment of depression demonstrated some improvements in depression scores with t-VNS; however, the lack of comparisons between groups limits conclusions that may be drawn. Additional RCT evidence is needed to permit conclusions about whether t-VNS is associated with improved outcomes for epilepsy, depression, or other conditions.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in January 2015 identified the following comparative studies of VNS that are currently enrolling patients (see Table 1).
Table 1: Ongoing Comparative Studies of VNS

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Trials No.</th>
<th>Planned Enrollment</th>
<th>Estimated Study Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninvasive Neurostimulation of the Vagus Nerve for the Treatment of Cluster Headache</td>
<td>NCT01792817</td>
<td>150</td>
<td>Jun 2014</td>
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<tr>
<td>A Randomized Multicenter Study for the Acute Relief of Episodic and Chronic Headache</td>
<td>NCT01958125</td>
<td>108</td>
<td>Mar 2014</td>
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<tr>
<td>Controlled Randomized Vagus Nerve Stimulation (VNS) Therapy Versus Resection (CoRaVNSTiR)</td>
<td>NCT02089243</td>
<td>40</td>
<td>Jul 2016 (follow-up through Jul 2017)</td>
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<tr>
<td>INcrease Of VAgal Tone in CHF (INOVATE-HF)</td>
<td>NCT01303718</td>
<td>650</td>
<td>Jun 2015</td>
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</tbody>
</table>

Summary of Evidence

For patients with refractory seizures, evidence from randomized controlled trials (RCTs) and multiple observational studies supports a reduction in seizure frequency following VNS. A TEC Assessment concluded that the evidence is sufficient to permit conclusions on the efficacy of this technique for treatment of refractory seizures. Therefore, VNS may be considered medically necessary for patients with refractory seizures.

For patients with depression, there is some evidence supporting improvements in depressive symptoms after VNS. However, there are a number of limitations of these data, including uncertain clinical significance, lack of evidence on durability, and lack of comparison with alternative treatments. As a result, it is not clear if VNS is as effective as alternatives for specific populations of patients with depression, and VNS is considered investigational for this indication.

For other conditions, including but not limited to headaches, obesity, essential tremor, heart failure, fibromyalgia, tinnitus, and traumatic brain injury, the evidence is limited and not sufficient to permit conclusions on efficacy. VNS is considered investigational for these indications.

The body of evidence for the use of t-VNS consists of small RCTs with methodologic limitations and case series. The evidence is insufficient to allow conclusions on the efficacy of t-VNS, and there are no transcutaneous stimulation devices that have U.S. FDA approval; therefore, transcutaneous VNS is considered investigational.

References

Vagus Nerve Stimulation

Policy #  00134
Original Effective Date:  06/05/2002
Current Effective Date:  11/16/2015


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Policy History

<table>
<thead>
<tr>
<th>Original Effective Date:</th>
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<tr>
<td>Current Effective Date:</td>
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<tr>
<td>03/21/2002</td>
<td>Medical Policy Committee review</td>
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<tr>
<td>06/05/2002</td>
<td>Managed Care Advisory Council approval</td>
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<tr>
<td>05/07/2004</td>
<td>Medical Director review</td>
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<td>05/18/2004</td>
<td>Medical Policy Committee review. Format revision. No substance change to policy.</td>
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<td>06/28/2004</td>
<td>Managed Care Advisory Council approval</td>
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<tr>
<td>06/07/2005</td>
<td>Medical Director review</td>
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<td>06/21/2005</td>
<td>Medical Policy Committee review. Clinical criteria revised to add investigational statement for VNS treatment for essential tremor</td>
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<td>07/15/2005</td>
<td>Managed Care Advisory Council Approval</td>
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<td>06/07/2006</td>
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<td>12/31/2010</td>
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Vagus Nerve Stimulation

Policy # 00134
Original Effective Date: 06/05/2002
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11/03/2011 Medical Policy Committee review
11/01/2012 Medical Policy Committee review
11/28/2012 Medical Policy Implementation Committee approval. Added heart failure and fibromyalgia to the list of investigational indications.
01/23/2013 Coding updated
11/07/2013 Medical Policy Committee review
11/20/2013 Medical Policy Implementation Committee approval. No change to coverage.
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. Policy statement updated to include the addition of tinnitus and traumatic brain injury to the list of investigational conditions. “Based on review of available data, the Company considers non implantable vagus nerve stimulation (VNS) devices for all indications to be investigational” was added to the investigational section.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2016 Coding update
Next Scheduled Review Date: 11/2016

Coding
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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Vagus Nerve Stimulation

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient’s illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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