Stimulation of the vagus nerve can be performed by means of an implantable stimulator within the carotid artery sheath. This technique has been proposed as a treatment for refractory seizures, depression, and other disorders. There are also devices available that are implanted at different areas of the vagus nerve. This policy addresses only devices implanted within the carotid sheath, and not to other types of devices. This evidence review also addresses devices that stimulate the vagus nerve transcutaneously.

Background

**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 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.

A type of VNS device addressed in this evidence review 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 intervals or on demand by patients or family by placing a magnet against the subclavicular implant site.
Various types of devices that stimulate the vagus nerve transcutaneously have been developed as well. One device made by Cerbomed stimulates the auricular branch of the vagus nerve. Some devices used in studies are not well characterized as to the specific manufacturer or type of device used. The U.S. Food and Drug Administration has not approved any transcutaneous VNS devices.

Other types of vagus nerve stimulators 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.

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.

**Regulatory Status**

In 1997, the U.S. Food and Drug Administration (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.”

On July 15, 2005, Cyberonics received PMA supplement approval by the 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.”

Cerbomed has developed a transcutaneous VNS (t-VNS®) 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 US. Electrocore has developed a non-invasive VNS (gammaCore®) that is currently being investigated for headache; the device does not have FDA approval.
Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Vagus nerve stimulation may be considered **medically necessary** as a treatment of medically refractory seizures.

Vagus nerve stimulation is considered **not medically necessary** as a treatment of other conditions, including but not limited to heart failure, fibromyalgia, depression, essential tremor, obesity, headaches, tinnitus, and traumatic brain injury.

Non-implantable vagus nerve stimulation devices are considered **investigational** for all indications.

Policy Guidelines

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.

Vagal nerve stimulation requires not only the surgical implantation of the device, but also subsequent neurostimulator programming, which occurs intraoperatively and typically during additional outpatient visits.

Rationale

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 (1) that offered the following conclusions.

- Published evidence from 2 large, well-designed multicenter trials involving over 300 patients demonstrates that the use of vagus nerve stimulation 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 vagus nerve stimulation 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 pharmacoresistant focal seizures, which supported the beneficial effects of VNS for this group. (2)
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.” (3) 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 that time are consistent with their 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 years’ follow-up. (4) 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. (5) 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. (6) 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 prior to VNS implantation. The reduction in seizure frequency was not statistically significantly different between subjects generalized and focal epilepsy.

VNS for Childhood Seizures

Since the 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. (7) For example, 60 pediatric patients were treated as part of the double-blind clinical trials conducted to support the FDA application. (8) 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, (9) and none resulted in termination of stimulation. Hornig and colleagues reported on a case series of 19 pediatric patients, with observation periods ranging up to 30 months. (10) 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 following VNS implantation, while 39% had 50% to 90% reduction. (11)

Healy et al. reported that among 16 patients under age 12 who underwent VNS implantation at a single center, 9 children (56%) experienced a reduction in their seizure frequency of 50% or more. (12) Results from an add-on study to a randomized controlled trial designed to compare high-output to low-output VNS stimulation among 41 children with medically refractory epilepsy suggest that VNS does not have adverse effects on cognitive or psychosocial outcomes. (13) 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, (14) a retrospective case-control study with 36 VNS patients compared with 72 age- and sex-matched controls with refractory epilepsy not treated with VNS, (15) a
retrospective cohort study including 252 pediatric patients with a variety of seizure types treated with VNS. (16) and a retrospective cohort study of 347 children with a variety of seizure types followed for up to 2 years postimplantation. (17)

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. (18) Tecoma and Iragui cite a multicenter retrospective analysis of 50 children with Lennox Gastaut syndrome (LGS) treated with VNS. (3) 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. (19) 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 Lennox Gastaut-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. (20)

VNS generally does not completely eliminate seizures, and it is not possible to predict which patients will 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. (21) In 2014, 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 a lesion on MRI predicted a good outcome. (22) These studies support the use of VNS in children, in patients with generalized epilepsy, and in those who are not candidates for surgery.

Section Summary: Treatment of Seizures
The evidence on the efficacy of VNS for treatment of refractory seizures consists of two 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 treatment-resistant depression is related to reports of improvement in depressed mood among epileptic patients undergoing VNS. (23) TEC Assessments written in 2005 and updated in 2006 concluded that evidence was insufficient to permit conclusions of the effect of VNS therapy on depression. (24, 25) 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. (26, 27) 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.

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 published before the randomized trial showed rates of improvement with VNS, 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. (29-31) 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. (27,28) 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 compared with sham treatment (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. (26,28) However, issues such as unmeasured differences among 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. (28) 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 Assessments, 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. (32) VNS was found to be associated with a reduction in depressive symptoms in the open-label studies. However, results from the only double-blind trial
were considered to be inconclusive. (27,28) 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 included in their analysis, 31.8% of subjects responded to VNS treatment. (33) 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 (34) 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 (35) (D-03), D-04, and Aaronson et al (D-21) study results. (36) 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 only) that were unpublished at the time of the meta-analysis publication (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 aged 65 years or older. (37) The authors identified 2 small studies that 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). (36) 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 group from baseline to the 22-week follow-up. At 50-week 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 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. (35) A small study of 9 patients with rapid-cycling bipolar disorder showed improvements in several depression rating scales over 40 weeks of observation. (38) 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. (39)
case series that included 27 patients with treatment-resistant depression, 5 patients demonstrated complete remission after 1 year and 6 patients were considered responders.\(^{(40)}\)

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 (eg, those with mania, hypomania, suicide, or worsening depression), there does not appear to be a greater risk of these events during VNS therapy. \(^{(28)}\)

**Section Summary: Treatment-Resistant Depression**
There is one 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 non-randomized 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 Chronic Heart Failure**

VNS has been investigated for treatment of chronic heart failure in some case series. A case series phase 2 trial of VNS therapy for chronic heart failure reported improvements in New York Heart Association class quality of life, 6-minute walk test, and left ventricular (LV) ejection fraction. \(^{(41)}\) The ANTHEM-HF study is also a case series study, but patients were randomized to either right- or left-sided vagus nerve implantation (but there was no control group). \(^{(42)}\) Overall, from baseline to 6-month follow-up, LV ejection fraction improved by 4.5% (95% CI, 2.4 to 6.6), LV end systolic volume improved by -4.1 mL (95% CI, -9.0 to 0.8), LV end-diastolic diameter (LVESD) improved by -1.7 mm (95% CI, -2.8 to -0.7), heart rate variability improved by 17 milliseconds (95% CI, 6.5 to 28), and 6-minute walk distance improved by 56 meters (95% CI, 37 to 75).

In 2015, Zannand et al reported results from the NECTAR-HF trial, a randomized, sham-controlled trial, with outcomes from VNS in patients with severe LV dysfunction, despite optimal medical therapy.\(^{(43)}\) Ninety-six patients were implanted with a vagal nerve stimulator and randomized in a 2:1 manner to active therapy (VNS ON) or control (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 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, ie, 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...
Treatment of Upper-Limb Impairment Due to Stroke

Dawson et al conducted a randomized pilot trial of VNS in patients with upper-limb dysfunction after ischemic stroke. (44) Twenty-one subjects were randomized to VNS plus rehabilitation or rehabilitation alone. Mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group versus +3.0 in the control group (p=0.064). Six patients in the VNS group achieved clinically meaningful response versus 4 in the control group (p=0.17).

Essential Tremor, Obesity, Headache, Fibromyalgia, and Tinnitus

VNS has been investigated with small pilot studies or studies evaluating mechanism of disease for several conditions. These conditions include essential tremor, (45) obesity,(46) fibromyalgia,(47) headache,(48,49) and tinnitus.(50) None of these studies are sufficient to make conclusions on the effect of VNS on these conditions. Only conditions for which at least 1 randomized trial has been reported will be detailed.

Section Summary: Other Conditions
In other conditions evaluated with RCTs (heart failure, upper-limb impairment), the trials did not show efficacy of VNS for the primary outcome. Other conditions (essential tremor, obesity, headache, fibromyalgia, tinnitus) have only been investigated with case series, which are not sufficient to make conclusions on the effect of VNS.

Transcutaneous VNS

Only conditions for which there is at least 1 RCT will be discussed, as case series are inadequate to determine the effect of the technology.

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. (51) 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 5/7 patients
reported a reduction in seizure frequency. (52) 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. (53)

**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. (54) 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.

Hasan et al reported a randomized trial of t-VNS for the treatment of schizophrenia. (55) 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 et al conducted a systematic review of studies evaluating the evidence related to transcutaneous trigeminal or VNS for psychiatric disorders. (56) 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 (52). The authors also include a fifth study in 1 data table, although not in their text or reference list (Hein et al, previously described(54) Overall, the studies included were limited by small size and poor generalizability.

**Transcutaneous VNS for Headache**

Gaul et al reported the results of a randomized open-label study of t-VNS for the treatment of chronic cluster headache. (57) Forty-eight patients with chronic cluster headache were randomized to either t-VNS or to individualized standard of care. Transcutaneous VNS was to be used twice daily with the option of additional treatment during headaches. At 4 weeks, the t-VNS group had a greater reduction in the number of headaches than the control group, resulting in a mean therapeutic gain of 3.9 fewer headaches per week (p=0.02). In terms of response rate, defined as a 50% or more reduction in headaches, the t-VNS group had a 40% response rate versus 8.3% in the control group (p<0.001). The study lacked a sham placebo control group, which may result in placebo response in the t-VNS group.

Goadsby et al reported results from an open-label pilot study of t-VNS for the treatment of migraine with or without aura.(58) 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 post treatment. Thirteen subjects reported adverse events, which were all considered mild or moderate.
Transcutaneous VNS for Impaired Glucose Tolerance

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. (59) 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
Transcutaneous VNS has been investigated with small randomized trials for several conditions. Some evidence for the efficacy of t-VNS for epilepsy comes from a 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 are problematic. In the study of depression, 1 small RCT that compared treatment with t-VNS with sham stimulation demonstrated some improvements in depression scores with t-VNS; however, the lack of comparisons between groups limits conclusions that may be drawn. An RCT for cluster headache showed a reduction in headache frequency, but did not have a sham treatment group. A sham-controlled pilot RCT for impaired glucose tolerance showed some effect on glucose tolerance tests.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

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<th>Trial Name</th>
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<th>Completion Date</th>
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<td>Prospective Randomized Controlled Study of Vagus Nerve Stimulation Therapy in the Patients With Medically Refractory Medial Temporal Lobe Epilepsy; Controlled Randomized Vagus Nerve Stimulation Versus Resection (CoRaVNStIR)</td>
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<td>A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore®, a Non-invasive Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache.</td>
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<td>Non-invasive Neurostimulation of the Vagus Nerve With the GammaCore Device for the Treatment of Cluster Headache</td>
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<td>Oct 2014</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

In 1999, the American Academy of Neurology (AAN) released a consensus statement on the use of VNS in adults that stated, “VNS is indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies."(60) The AAN released an update to these guidelines in 2013 that stated, “VNS may be considered for seizures in children, for LGS [Lennox-Gastaut-syndrome]-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C).”(61)

The American Psychiatric Association guidelines on the treatment of major depressive disorder in adults, updated in November 2010, includes the following statement on the use of VNS: “Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [Electroconvulsive therapy],” with a level of evidence III (May be recommended on the basis of individual circumstances). (62)

In 2013, the European Headache Federation issued a consensus statement on neuromodulation treatments for chronic headaches, which makes the following statement about the use of VNS: “Due to the lack of evidence, VNS should only be employed in chronic headache sufferers using a randomized, placebo controlled trial design.”(63)

U.S Preventive Services Task Force Recommendations

Not applicable.

Summary of Evidence

The evidence for vagus nerve stimulation (VNS) in individuals who have seizures refractory to medical treatment includes randomized controlled trials (RCTs) and multiple observational studies. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs 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 evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for VNS in individuals who have treatment-resistant depression includes 1 RCT and other nonrandomized comparative studies and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT reported only short-term results and found no significant improvement for the primary outcome. Other available studies are limited by small sample sizes, potential selection bias, and lack of a control group in the case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for VNS in individuals who have chronic heart failure or upper-limb impairment due to stroke includes RCTs and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs for both conditions did not show significant improvements in the primary outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.
The evidence for VNS in individuals who have essential tremor, obesity, headache, fibromyalgia, or tinnitus includes case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Case series are insufficient to make conclusions regarding efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for transcutaneous VNS stimulation in individuals who have epilepsy, depression, schizophrenia, headache, or impaired glucose tolerance includes at least 1 RCT and case series for some of the conditions. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs are all small and have various methodologic problems. None shows definitive efficacy of transcutaneous VNS in improving outcomes among patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Medicare Policy**

Medicare has a national coverage determination for vagus nerve stimulation. 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. (64)

**References**

62. Association AP. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 2010; 3rd


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<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>September 2012</td>
<td>New Policy</td>
<td>Policy updated with literature review; Policy statement unchanged.</td>
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<tr>
<td>June 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review adding references 7, 13-17, 29-31, and 41-44. Policy statement updated to include the addition of tinnitus and traumatic brain injury to the list of not medically necessary conditions. Rationale section reorganized.</td>
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Keywords

NCP®
NeuroCybernetic Prosthesis (NCP)
Vagus Nerve Stimulation
VNS

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 24, 2016 and is effective July 15, 2016.

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