Vagus Nerve Stimulation

Policy # 00134
Original Effective Date: 06/05/2002
Current Effective Date: 12/20/2017

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 events 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 depression, heart failure, upper limb impairment due to stroke, essential tremor, headaches, fibromyalgia, tinnitus, and traumatic brain injury to be **investigational.***

Based on review of available data, the Company considers transcutaneous (nonimplantable) 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 include generalized seizures, and it has been investigated for a range of other conditions.

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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 transcutaneously stimulate the vagus nerve have been developed as well. The U.S. Food and Drug Administration (FDA) has not approved any transcutaneous VNS devices.

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.

Indications
VNS was originally approved for the treatment of medically refractory epilepsy. Significant advances have been made since then in the surgical and medical treatment of epilepsy, and newer, more recently approved medications are available. Despite these advances, however, 25% to 50% of patients with epilepsy experience breakthrough seizures or suffer from debilitating adverse effects of antiepileptic drugs. For patients such as these, VNS therapy has been used as an alternative or adjunct to epilepsy surgery or medications.

Based on observations that patients treated with VNS experience 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 heart failure, headaches, tremor, fibromyalgia, tinnitus, and traumatic brain injury.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In 1997, the NeuroCybernetic Prosthesis (NCP®)‡ System (Cyberonics, Houston, TX), a VNS device, was approved by FDA through the premarket approval process 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." There have been subsequent expanded approvals. FDA product code: LYF

On May 30, 2017, the gammaCore-S®‡ (electroCore LLC, Basking Ridge, NJ), a noninvasive VNS device, was cleared for marketing through the 510(k) process (K171306) for the acute treatment of adults with episodic cluster headaches. When the device is applied to the side of the neck by the patient, a mild electrical stimulation of the vagus nerve is carried to the central nervous system. Each stimulation using gammaCore-S lasts 2 minutes. The patient controls the stimulation strength. FDA product code: PKR

Cerbomed (Erlangen, Germany) 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 electrical stimulation for several hours a day; no surgical procedure is required. The device received the CE mark in Europe in 2011, but has not been FDA-approved for use in the United States. ElectroCore Medical has developed a noninvasive VNS system (gammaCore®)‡ that is currently being investigated for headache; the device has not been FDA-approved for use in the United States.

Table 1 includes the updates pertinent to this evidence review.

Table 1. FDA-Approved or -Cleared Vagus Nerve Stimulators

Device Name	Manufacturer	Date Cleared	PMA/510(k)	Indications
NeuroCybernetic Prosthesis (NCP)	Cyberonics	1997	P970003	Indicated or adjunctive treatment of adults and adolescents >12 years of age with medically refractory partial onset seizures
		Jul 2005	P970003/S50	Expanded indication for adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 years of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments
		Jun 2017	P970003/S207	Expanded indicated use as adjunctive therapy for seizures in patients ≥4 years of age with partial-onset seizures that are refractory to antiepileptic medications
gammaCore	ElectroCore	May 2017	K171306	Indicated for acute treatment of pain associated with episodic cluster headache in adults using noninvasive VNS on the side of the neck

FDA: Food and Drug Administration; PMA: premarket approval; VNS: vagus nerve stimulation.

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

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures, also known as surrogate outcome measures, may also be adequate if there is an established link between the intermediate outcome and true health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes, but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

TREATMENT OF TREATMENT-RESISTANT SEIZURES

Clinical Context and Test Purpose
The purpose of implantable VNS is to apply pulsed electrical energy via the vagus nerve to alter aberrant neural activity resulting in seizures.

The question addressed in this evidence review is this: Does the use of VNS as a treatment for medically refractory seizures result in changes in management and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
One relevant population of interest is patients with medically refractory seizures.

Interventions
The intervention of interest is implantable VNS.

Comparators
Comparators are conventional antiepileptic drugs and/or resective surgery.

Outcomes
Outcomes of interest are technical reliability, clinical validity or diagnostic accuracy (test accuracy, test validity [eg, sensitivity, specificity]), and clinical utility that includes consideration of avoidance of harms.

Timing
VNS is typically used when a patient has had unsuccessful medical therapy, been intolerant of medical therapy, or had failed resective surgery.

Setting
VNS is initiated with surgical implantation and subsequently administered in outpatient and home care settings.

Systematic Reviews
Reports on the use of VNS to treat medication-resistant seizure disorders date to the 1990s and were coincident with preapproval and early postapproval study of the device.

VNS for Adult Partial-Onset Seizures
In 2011, Englot et al published a meta-analysis of the literature through November 2010 on the efficacy of VNS and its predictors of response. Table 2 summarizes the 15 RCTs or prospective observational studies. Overall, VNS predicted a 50% or greater reduction in seizure frequency at last follow-up, the main effect, with an odds ratio of 1.83 (95% confidence interval [CI], 1.80 to 1.86; p<0.001). Table 2 summarizes the meta-analysis.

Table 2. Summary of Trials and Studies Included in Meta-Analysis

Study (Year)	N	Duration FU	No. of Sites	Design	Seizure Type	Seizure Frequency Reduction >50%, %
Ben-Menachem et al (1994)	114	3 mo	Multisite	Blinded RCT	Partial	31
Handforth et al (1998)	196	3 mo	Multisite	Blinded RCT	Partial	23
Amar et al (1998)	17	3 mo	Single	Blinded RCT	Partial	57
Scherrmann et al (2001)	29	NR	Single	Nonblinded RCT	Mixed	45
DeGiorgio et al (2005)	61	3 mo	Multisite	Nonblinded RCT	Partial	29
Ben-Menachem et al (1999)	64	3-64 mo	Single	Prospective OBS	Mixed	45
Parker et al (1999)	15[a]	1 y	Single	Prospective OBS	Mixed	27
Labar et al (1999)	24	3 mo	Single	Prospective OBS	Generalized	46
DeGiorgio et al (2000)	195	12 mo	Multisite	Prospective OBS	Mixed	35
Chavel et al (2003)	29	1-2 y	Single	Prospective OBS	Partial	54[b]
Vonck et al (1999; 2004)	118	> 6 mo	Multisite	Prospective OBS	Mixed	50
Majoie et al (2001; 2005)	19[a]	2 y	Single	Prospective OBS	Mixed	21
Huf et al (2005)	40[c]	2 y	Single	Prospective OBS	NR	28
Kang et al (2006)	16[d]	>1 y	Multisite	Prospective OBS	Mixed	50
Ardesch et al (2007)	19	>2 y	Single	Prospective OBS	Partial	33[e]

FU: follow-up; NR: not reported: OBS: observational; RCT: randomized controlled trial.
[a] Children with encephalopathy.
[b] Rate at 1-year follow-up.
[c] Adults with low IQ.
[d] Children.
[e] Rate at 2 years.

This evidence review was informed, in part, by a 1998 TEC Assessment on treatment of seizures that offered the following conclusions:

- For patients 12 years of age and older with medically refractory partial-onset seizures, for whom surgery is not recommended or for whom surgery has failed evidence, is available from 2 multicenter, randomized, blinded, active control studies submitted for device registration. The trials, which were limited to patients with partial-onset seizures, and included outcomes for 314 patients, presented sufficient data to demonstrate that VNS is a beneficial adjunct to optimal anti-epileptic drug therapy for the treatment of these seizures. In patients with at least 6 partial-onset seizures per month, VNS reduced seizure frequency by approximately 25% after 3 months of treatment. In patients who achieved an initial reduction in seizure frequency, the beneficial treatment effect appeared to be maintained and may increase with time. The results of these studies are included in Table 2.
- Adverse events were mild and consisted primarily of hoarseness or voice change during “on” periods of stimulation.

Based on this TEC Assessment, earlier versions of this evidence review supported the use of VNS for partial-onset seizures for patients older than 12 years of age in individuals for whom surgery is not recommended or for whom surgery has failed.

In 2015, Panebianco et al updated a Cochrane systematic review and meta-analysis of VNS to treat partial seizures. Reviewers specifically evaluated randomized, double-blind, parallel or crossover, controlled trials of VNS as add-on treatment comparing high- and low-stimulation paradigms and VNS stimulation vs no stimulation or a different intervention. Five trials (total N=439 participants) compared high-frequency stimulation with low-frequency stimulation in participants ages 12 to 60 years, and another trial examined high-frequency stimulation vs low-frequency stimulation in children. The overall relative risk for a response to high stimulation compared with low stimulation using the fixed-effect model was calculated to be 1.73 (95% CI, 1.13 to 2.64; p=0.01), showing that patients receiving high stimulation were more likely to show a 50% or greater reduction in seizure frequency.

Randomized Controlled Trials
In 2014, Ryvlin et al reported on an RCT on long-term quality of life outcomes for 112 patients with medication-resistant focal seizures, which supported the beneficial effects of VNS for this group.

VNS for Adult Generalized Seizures
Resective surgery is a less attractive therapeutic option for individuals with generalized treatment-resistant seizures that may be multifocal or involve an eloquent area. VNS has been evaluated as an alternative to disconnection procedures such as surgical division of the corpus callosum.

The evidence for the efficacy of VNS for generalized seizures in adults is primarily from observational data, including registries and small cohort studies.

In 2016, Englot et al examined freedom from seizure rates and predictors across 5554 patients enrolled in the VNS Therapy Patient Outcomes Registry. The registry was established in 1999, after the 1997 U.S. FDA approval of VNS and is maintained by the manufacturer of the device, Cyberonics (Houston, TX). Data were prospectively collected by 1285 prescribing physicians from 978 centers (911 in the United States and Canada and 67 internationally) at patients' preoperative baselines and various intervals during therapy. During active data collection, participation in the registry included approximately 18% of all implanted VNS devices. The database was queried in January 2015, and all seizure outcomes reported with the 0- to 4-, 4- to 12-, 12- to 24-, and 24- to 48-month time ranges after VNS device implantation were extracted and compared with patient preoperative baseline. Available information was tracked at each time point of data submission for the following outcomes: patient demographics, epilepsy etiology and syndrome, historical seizure types and frequencies, quality of life, physician global assessment, current antiepileptic drugs, medication changes, malfunctions, battery changes, and changes in therapy. At each observation time point, responders were defined as having a 50% or greater decrease in seizure frequency compared with baseline and nonresponders as less than a 50% decrease.

A localized epilepsy syndrome such as partial-onset seizures was recorded in 59% of the registry participants, generalized epilepsy in 27%, and 11% had a syndromic etiology (eg, Lennox-Gastaut).

The outcomes for the approximately 1500 registry enrollees with generalized seizures are summarized in Table 3. These rates did not differ statistically from participants with predominantly partial seizures.

Table 3. Summary of VNS Registry Outcome Results

Generalized Seizures	Responder Rate, %	Seizure Freedom Rate, %
0-4 mo	50	7
4-12 mo	55	8
12-24 mo	55	8
24-48 mo	≈60[a]	≈9[a]

Responder rate: ≥50% decrease in seizure frequency; VNS: vagus nerve stimulation.
[a] Approximation based on publication Figure 1 and narrative.

In 1999, Labar reported a 46% response rate (see Table 2). In 2007, Kostov reported seizure reduction of 61% in a case series of 12 patients with drug-resistant idiopathic generalized epilepsy. In 2013, Garcia-Navarrete et al evaluated outcomes after 18 months of follow-up for a prospectively followed cohort of 43 patients with medication-resistant epilepsy who underwent VNS implantation. Subjects' seizure types were heterogeneous, but 52% had generalized epilepsy. Pharmacotherapy was unchanged during the study. Twenty-seven (63%) subjects were described as "responders," defined as having a 50% or greater reduction in seizure frequency compared with the year before VNS implantation. The difference in reduction of seizure frequency was not statistically significant between subjects with generalized and focal epilepsy.

VNS for Pediatric Seizures

The evidence for VNS for pediatric seizures consists of a variety of small noncomparator trials, prospective observational studies, and retrospective case series. As in the adult studies, there is heterogeneity of

seizure etiologies: mixed, syndromic, and idiopathic; there is also generalized and limited information on concomitant antiepileptic drug requirement. Some studies have defined pediatric as less than 12 years of age and others have defined it as less than 18 years and may have included patients as young as 2 to 3 years of age. Study subpopulations may have had prior failed resective surgery. Complete freedom from seizures is the exception, and the primary reported end point is 50% or more reduction in seizure frequency, determined over varying lengths of follow-up. There is an overlap of authors for multiple studies suggesting utilization of VNS in specialized clinical care environments. Multiple studies have some form of innovator device company sponsorship.

Table 4 summarizes the evaluable literature on VNS in pediatric populations of all seizure types.

Table 4. Summary of VNS Pediatric Studies

Author (Year)	Study Type	Sample	Seizure Disorder Type	Duration of FU	Seizure Frequency Reduction ≥50% or Median Reduction, n (%)[a]	Notes
Hornig et al (1997)	Case series	19	Mixed	2-30 mo	10 (53)	Prior failed resective surgery: n=3
Murphy et al (1999)	Prospective OBS	60	Mixed	18 mo	46 (42)[a]	Age: 26% <12 y
Patwardhan et al (2000)	Case series	38	Mixed	12 mo (median)	26 (68)	Age: 11 mo to 16 y
Frost et al (2001)	Retrospective case review	50	LGS	6 mo	50 (57.9%[a]	Age: 13 y (median)
You et al (2007)	Prospective OBS	28	Mixed	31.4 mo (mean)	15 (53.6)	Age range: 2-17 y
Klinkenberg et al (2012)	RCT[b]	41	Mixed	19 wk	High-stim 3/21(14.2) Low-stim 4/20 (20)	Age range: 3-17 y
Cukiert et al (2013)	Case series	24	LGS	24 mo	NR[c]	Age: <12 y
Healy et al (2013)	Retrospective case review	16	Unknown	3-y review period	9 (56)	Age: <12 y
Terra et al (2014)	Retrospective case-control[d]	36	Mixed	3-y review period	20 (55.4) VNS group	Age: <18 y Difference from baseline seizure frequency[e]
Yu et al (2014)	Retrospective case review	69/252[f]	Mixed	12 mo	28 (40.6)	Age: <12 y=28

FU: follow-up; LGS: Lennox-Gastaut syndrome; NR: not reported; OBS: observational; RCT: randomized controlled trial; VNS: vagus nerve stimulation.

[a] Median reduction in total seizure frequency.
[b] RCT comparing high- (n=21) with low-stimulation (n=20) VNS.
[c] Seizure reduction not reported but 10 (41.6%) experienced transient seizure frequency worsening.
[d] Age-matched 31 VNS with 72 non-VNS controls.

[e] Baseline seizure frequency; VNS: 346.64 (SD=134.11) vs control group: 83.63 (SD=41.43). [f] Sixty-nine of 252 of identified cases had evaluable pre- and postimplantation data.

Section Summary: Treatment of Treatment-Resistant Seizures
The evidence on the efficacy of VNS for treatment of medically refractory seizures consists of 2 RCTs reported at the time of initial U.S. FDA approval of the marketed device, two recent meta-analysis, and numerous uncontrolled studies. The RCTs both reported a significant reduction in seizure frequency with VNS for patients with partial-onset seizures. The uncontrolled studies and case series have consistently reported reductions of clinical significance defined as a 50% or more reduction in seizure frequency in both adults and children over almost 2 decades of publications. Interpretation of all outcomes and results were limited by the variety of comparators (when used), variability in length of follow-up, limited published data on antiepileptic medication requirements, mixed seizure etiologies, and history of prior failed resective surgery. There is an overlap of authors across multiple studies, suggesting utilization of VNS in specialized clinical care environments. Multiple studies have some form of innovator device company sponsorship.

TREATMENT-RESISTANT 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. TEC Assessments written in 2005 and updated in 2006 concluded that evidence was insufficient to permit conclusions about the effect of VNS therapy on depression. 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 randomized trial 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 events 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. 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 vs 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%) compared with sham treatment (7.5%; p=0.04).

The observational study that compared patients participating in the RCT with patients in 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 among patients, nonconcurrent controls, differences in sites of care between VNS therapy patients and controls, and differences in 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 Assessments, several systematic reviews and meta-analyses have assessed the role of VNS in treatment-resistant depression. A 2008 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-label studies. However, results from the only double-blind trial were considered to be inconclusive. Daban et al (2008) 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 (2012) reported that among the uncontrolled studies included 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 on results from a 2013 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 (2010) (D-03), D-04, and Aaronson et al (D-21) study (2013) results. Also, the meta-analysis used data from a registry of patients with treatment-resistant depression (335 patients receiving VNS plus 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 reported that adjunctive VNS was associated with a greater likelihood of treatment response (odds ratio, 3.19; 95% 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. Reviewers 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 on 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 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 (2010) 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 2008 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 (2011) 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 that included 27 patients with treatment-resistant depression, 5 patients demonstrated complete remission after 1 year, and 6 patients were considered responders.

Adverse events 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.

Section Summary: Treatment-Resistant Depression
There is an RCT evaluating the efficacy of VNS for treatment-resistant depression. This trial 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 sample sizes and the potential for selection bias; the case series are further limited by the lack of control

groups. 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 on the effect of this technology on major depression.

OTHER CONDITIONS

Treatment of Chronic Heart Failure

VNS has been investigated for the treatment of chronic heart failure in some case series. A 2011 phase 2 case series 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. The ANTHEM-HF study (2014) is another case series, but in it patients were randomized to right- or left-sided vagus nerve implantation (but there was no control group). Overall, from baseline to 6-month follow-up, a number of measures were improved: 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 mL); LV end-diastolic diameter improved by -1.7 mm (95% CI, -2.8 to -0.7 mm); heart rate variability improved by 17 ms (95% CI, 6.5 to 28 ms); and 6-minute walk distance improved by 56 meters (95% CI, 37 to 75 meters).

In 2015, Zannand et al reported on results from NECTAR-HF, a randomized, sham-controlled trial, with outcomes from VNS in patients with severe LV dysfunction despite optimal medical therapy. 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 the 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 LV end-diastolic diameter from baseline to 6 months, there were no significant differences between groups (p=0.60 between-group difference in LV end-diastolic diameter 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 group; p=0.02). Subject blinding was found to be imperfect, which may have biased the subjective outcome data reporting.

Treatment of Upper-Limb Impairment due to Stroke

Dawson et al (2016) conducted a randomized pilot trial of VNS in patients with upper-limb dysfunction after ischemic stroke. 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 clinically meaningful response and 4 in the control group (p=0.17).

ESSENTIAL TREMOR, HEADACHE, FIBROMYALGIA, TINNITUS, AND AUTISM
VNS has been investigated with small pilot studies or studies evaluating the mechanism of disease for several conditions. These conditions include essential tremor, fibromyalgia, headache, and tinnitus. The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited but there are no RCTs. None of these studies are sufficient to make conclusions on the effect of VNS on these conditions.

Section Summary: Other Conditions
In other conditions evaluated with RCTs (heart failure, upper-limb impairment), the trials failed to show the efficacy of VNS for the primary outcome. Other conditions (essential tremor, headache, fibromyalgia, tinnitus, autism) 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, because case series are inadequate to determine the effect of the technology.

Epilepsy
Aihua et al (2014) reported on results from a series of 60 patients with pharmaco-resistant epilepsy treated with a transcutaneous VNS (t-VNS) device, who were randomized to stimulation over the earlobe (control group) or the Ramsay-Hunt zone (treatment group), 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 events (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 months vs 6.0 months; $p<0.001$) and 12 months (4.0 months vs 6.0 months; $p<0.001$) 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 months vs 8.0 months; $p<0.001$).

Two small case series were identified that used a t-VNS device for treatment of medication-refractory seizures. In a small case series of 10 patients with treatment-resistant epilepsy, Stefan et al (2012) reported that 3 patients withdrew from the study, while 5 of 7 patients reported a reduction in seizure frequency.[68] In another small case series, He et al (2013) reported that among 14 pediatric patients with intractable epilepsy who were treated with bilateral t-VNS, of the 13 patients who completed follow-up, the 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.

Psychiatric Disorders
Hein et al (2013) reported on results of 2 pilot RCTs of a t-VNS device for the treatment of depression, 1 which included 22 subjects and 1 with 15 subjects. In the first study, 11 subjects 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 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, 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 points ($p<0.05$) after 2 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 et al (2015) reported a randomized trial of t-VNS for the treatment of schizophrenia. 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 (2014) conducted a systematic review of studies evaluating the evidence related to transcutaneous stimulation of the trigeminal or vagus nerve for psychiatric disorders. They found 4 studies addressing t-VNS for psychiatric disorders (total N=84 subjects). Three of the 4 studies evaluated physiologic parameters in healthy patients, and one evaluated pharmaco-resistant epilepsy (Stefan et al, previously described). Reviewers also include a fifth study in a data table, although not in their text or reference list (Hein et al, previously described). Overall, the studies included were limited by small size and poor generalizability.

Headache
Gaul et al (2016) reported the results of a randomized open-label study of t-VNS for the treatment of chronic cluster headache. Forty-eight patients with chronic cluster headache were randomized to 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 ($p=0.02$). Regarding response rate, defined as a 50% or more reduction in headaches, the t-VNS group had a 40% response rate, and the control group had an 8.3% response rate ($p<0.001$). The study lacked a sham placebo control group, which may result in placebo response in the t-VNS group.

Goadsby et al (2014) reported on 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.

Impaired Glucose Tolerance
Huang et al (2014) reported on results of a pilot RCT of a t-VNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance. The trial 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 mmol/L 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, a 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 randomized trial for impaired glucose tolerance showed some effect on glucose tolerance tests.

SUMMARY OF EVIDENCE

Vagus Nerve Stimulation

For individuals who have seizures refractory to medical treatment who receive VNS, the evidence includes RCTs and multiple observational studies. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs have 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 that the technology results in a meaningful improvement in the net health outcome.

For individuals who have treatment-resistant depression who receive VNS, the evidence includes an RCT and other nonrandomized comparative studies and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT only reported 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.

Other Conditions

For individuals who have chronic heart failure who receive VNS, the evidence 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.

For individuals who have upper-limb impairment due to stroke who receive VNS, the evidence includes a single pilot study. Relevant outcomes are symptoms, change in disease status, and functional outcomes. There was preliminary support for improvement in functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have other neurologic conditions (eg, essential tremor, headache, fibromyalgia, tinnitus, or autism) who receive VNS, the evidence 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.

Transcutaneous Vagus Nerve Stimulation
For individuals who have other neurologic, psychiatric, or metabolic disorders (eg, epilepsy, depression, schizophrenia, headache, impaired glucose tolerance) who receive transcutaneous VNS, the evidence includes RCTs 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 showed definitive efficacy of transcutaneous VNS in improving outcomes among patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 06/05/2002
Current Effective Date: 12/20/2017

03/21/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. No substance change to policy.

Vagus Nerve Stimulation

Policy # 00134
Original Effective Date: 06/05/2002
Current Effective Date: 12/20/2017

06/28/2004	Managed Care Advisory Council approval
06/07/2005	Medical Director review
06/21/2005	Medical Policy Committee review. Clinical criteria revised to add investigational statement for VNS treatment for essential tremor
07/15/2005	Managed Care Advisory Council Approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged
08/04/2006	Medical Director Review
08/09/2006	Medical Policy Committee approval
11/07/2007	Medical Director Review
11/15/2007	Medical Policy Committee approval. Added headaches to the investigational policy statement.
11/05/2008	Medical Director Review
11/18/2008	Medical Policy Committee approval. No change to coverage eligibility.
11/12/2009	Medical Policy Committee approval
11/18/2009	Medical Policy Implementation Committee approval. Deleted “partial-onset” verbiage from “medically refractory seizures” in the coverage section. Added the treatment of obesity as an investigational indication.
11/04/2011	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/31/2010	Coding updated.
11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 12/2018

Vagus Nerve Stimulation

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code			
CPT	0312T, 0313T, 0314T, 0315T, 0316T, 0317T, 61885, 61886, 61888, 64553, 64568, 64569, 64570, 95974, 95975			
HCPCS	C1767, C1778, C1787, C1816, C1820, C1822, C1883, L8679, L8680, L8681, L8682, L8683, L8685, L8686, L8687, L8688, L8689, L8695			
ICD-10 Diagnosis	G40.101-G40.119	G40.501-G40.509	G40.801-G40.814	G40.822-G40.89
	G40.901-G40.919	G40.B01-G40.B19	G43.109	H35.361-G35.369
	H93.11-G93.19	N39.3	O90.6	O99.315
	O99.345	R27.0-R27.9	R33.9	R34
	R35.0	R39.15	R39.19	S09.10XA
	S09.11XA	S09.19XA	S09.8XXA	S09.90XA

*****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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.