

Medical Policy



Title: Vagus Nerve Stimulation

Professional

Original Effective Date: June 1, 1997
 Revision Date(s): November 1, 1997;
 July 1, 1998; January 1, 2006;
 September 1, 2006; October 26, 2010;
 March 3, 2011; January 1, 2012;
 August 24, 2012; June 26, 2013;
 November 24, 2015; April 25, 2016;
 December 21, 2017; May 9, 2018;
 January 1, 2019

Current Effective Date: December 21, 2017

Institutional

Original Effective Date: April 1, 2007
 Revision Date(s): November 29, 2010;
 March 3, 2011; January 1, 2012;
 August 24, 2012; June 26, 2013;
 November 24, 2015; April 25, 2016;
 December 21, 2017; May 9, 2018;
 January 1, 2019

Current Effective Date: December 21, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • With seizures refractory to medical treatment	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: antiepileptic drugs or resective surgery	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With treatment-resistant depression	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: antidepressant drugs	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes

Populations	Interventions	Comparators	Outcomes
Individuals: • With chronic heart failure	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: medication management and physical rehabilitation	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With upper-limb impairment due to stroke	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: medication management and physical rehabilitation	Relevant outcomes include: • Symptoms • Change in disease status Functional outcomes
Individuals: • With other neurologic conditions (eg, essential tremor, headache, fibromyalgia, tinnitus, autism)	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: medication and behavioral therapy	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With episodic cluster headache	Interventions of interest are: • Transcutaneous vagus nerve stimulation	Comparators of interest are: • Standard of care: medication	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With other neurologic, psychiatric, or metabolic disorders	Interventions of interest are: • Transcutaneous vagus nerve stimulation	Comparators of interest are: • Standard of care: medication and behavioral therapy	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes

DESCRIPTION

Stimulation of the vagus nerve can be performed using a pulsed electrical stimulator implanted 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 evidence review also addresses devices that stimulate the vagus nerve transcutaneously.

Objective

The objective of this evidence review is to evaluate whether the use of vagus nerve stimulation to treat seizure disorders, depression, and other cardiovascular and neurologic conditions improves the net health outcomes.

Background

Vagus Nerve Stimulation

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. An electrical stimulus is

applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract.

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 these patients, 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.

Regulatory Status

In 1997, the NeuroCybernetic Prosthesis (NCP®) System (Cyberonics), a vagus nerve stimulation (VNS) device, was approved by FDA through the premarket approval (PMA) 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.”¹ There have been subsequent expanded approvals. FDA product code: LYF

In May 2015, a related VNS therapy, AspireSR® (LivaNova), received supplemental premarketing approval from FDA, although the device was recalled in August 2017.² The AspireSR® device detects high heart rates associated with seizures and responds with stimulation. Adjunctive use of the AspireSR® for the treatment of epileptic seizures was indicated for patients over 4 years of age who suffer from partial-onset seizures that do not respond to antiepileptic medication.

On May 2017, the gammaCore-S® (electroCore), a noninvasive VNS device, was cleared for marketing by FDA through the 510(k) process (K171306) for the acute treatment of adults with episodic cluster headaches.³ When the device is applied to the side of the neck by the patient, 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 electric stimulation for several hours a day; no surgical procedure is required. The device received the CE mark in Europe in 2011, but has not been FDA approved for use in the United States.

Table 1 includes the updates on stimulators pertinent to this evidence review.

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

Device Name	Manufacturer	Cleared	PMA/510(k)	Indications
NeuroCybernetic Prosthesis (NCP®)	Cyberonics	1997	P970003	Indicated or adjunctive treatment of adults and adolescents >12 y of age with medically refractory partial onset seizures
		2005	P970003/S50	Expanded indication for adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 y of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments
		2017	P970003/S207	Expanded indicated use as adjunctive therapy for seizures in patients ≥4 y of age with partial-onset seizures that are refractory to antiepileptic medications
gammaCore®	ElectroCore	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.

POLICY

- A. Vagus nerve stimulation may be considered **medically necessary** as a treatment of medically refractory seizures.
- B. Vagus nerve stimulation is considered **experimental / investigational** as a treatment of other conditions, including but not limited to depression, heart failure, upper-limb impairment due to stroke, essential tremor, headaches, fibromyalgia, tinnitus, and traumatic brain injury.
- C. Transcutaneous (nonimplantable) vagus nerve stimulation devices are considered **experimental / 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.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through December 11, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

Vagus Nerve Stimulation

Clinical Context and Test Purpose

The purpose of implantable vagus nerve stimulation (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

The relevant population of interest is patients with medically refractory seizures.

Interventions

The test being considered is implantable VNS.

Comparators

The following practices are currently being used: conventional antiepileptic drugs and/or resective surgery.

Outcomes

Outcomes of interest are 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.

Treatment-Resistant Seizures

VNS for Adult Partial-Onset Seizures

Englot et al (2011) conducted a meta-analysis of the literature through November 2010 assessing the efficacy of VNS and its predictors of response.⁴ Table 2 summarizes the 15 RCTs and prospective observational studies selected. 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. Summary of Trials and Studies Included in Meta-Analysis

Study (Year)	N	Duration of FU	No. of Sites	Design	Seizure Type	Seizure Frequency Reduction >50%, %
Ben-Menachem et al (1994) ⁵	114	3 mo	Multisite	Blinded RCT	Partial	31
Handforth et al (1998) ⁶	196	3 mo	Multisite	Blinded RCT	Partial	23
Amar et al (1998) ⁷	17	3 mo	Single	Blinded RCT	Partial	57
Scherrmann et al (2001) ⁸	29	NR	Single	Nonblinded RCT	Mixed	45
DeGiorgio et al (2005) ⁹	61	3 mo	Multisite	Nonblinded RCT	Partial	29
Ben-Menachem et al (1999) ¹⁰	64	3-64 mo	Single	Prospective OBS	Mixed	45
Parker et al (1999) ¹¹	15 ^a	1 y	Single	Prospective OBS	Mixed	27
Labar et al (1999) ¹²	24	3 mo	Single	Prospective OBS	Generalized	46
DeGiorgio et al (2000) ¹³	195	12 mo	Multisite	Prospective OBS	Mixed	35
Chavel et al (2003) ¹⁴	29	1-2 y	Single	Prospective OBS	Partial	54 ^b
Vonck et al (1999 ¹⁵ ; 2004 ¹⁶)	118	> 6 mo	Multisite	Prospective OBS	Mixed	50
Majoie et al (2001 ¹⁷ ; 2005 ¹⁸)	19 ^a	2 y	Single	Prospective OBS	Mixed	21
Huf et al (2005) ¹⁹	40 ^c	2 y	Single	Prospective OBS	NR	28
Kang et al (2006) ²⁰	16 ^d	>1 y	Multisite	Prospective OBS	Mixed	50
Ardesch et al (2007) ²¹	19	>2 y	Single	Prospective OBS	Partial	33 ^e

Adapted from Englot et al (2011).⁴

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 the treatment of seizures that offered the following conclusions²²:

- 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.^{5,6} 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 antiepileptic 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 has not been recommended or for whom surgery has failed.

Panebianco et al (2015) updated a Cochrane systematic review and meta-analysis of VNS to treat partial seizures.²³ Reviewers specifically evaluated randomized, double-blind, parallel or crossover, controlled trials of VNS as add-on treatment comparing high- and low-stimulation paradigms plus VNS stimulation with no stimulation or a different intervention. Five trials (n=439 participants) compared high-frequency stimulation with low-frequency stimulation in participants ages 12 to 60 years, and another trial compared high-frequency stimulation with low-frequency stimulation in children.^{6,9,24-26} 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

Ryvlin et al (2014) 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.²⁷

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.

Englot et al (2016) examined freedom from seizure rates and predictors across 5554 patients enrolled in the VNS Therapy Patient Outcomes Registry.²⁸ The registry was established in 1999, after the 1997 U.S. Food and Drug Administration approval of VNS, and is maintained by the manufacturer of the device, Cyberonics. 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 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 Outcomes

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

VNS: vagus nerve stimulation.

^a Responder rate: ≥50% decrease in seizure frequency.

^b Approximation based on publication Figure 1 and narrative.

Garcia-Navarrete et al (2013) evaluated outcomes after 18 months of follow-up for a prospective cohort of 43 patients with medication-resistant epilepsy who underwent VNS implantation.²⁹ 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 patients as less than 12 years of age and others have defined them 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	SFR ≥50% or Median Reduction, n (%) ^a	Notes
Hornig et al (1997) ³⁰	Case series	19	Mixed	2-30 mo	10 (53)	Prior failed resective surgery: n=3
Murphy et al (1999) ³¹	Prospective OBS	60	Mixed	18 mo	46 (42) ^a	Age: 26% <12 y
Patwardhan et al (2000) ³²	Case series	38	Mixed	12 mo (median)	26 (68)	Age: 11 mo to 16 y

Author (Year)	Study Type	Sample	Seizure Disorder Type	Duration of FU	SFR \geq 50% or Median Reduction, n (%) ^a	Notes
Frost et al (2001) ³³	Retrospective case review	50	LGS	6 mo	50 (57.9) ^a	Age: 13 y (median)
You et al (2007) ³⁴	Prospective OBS	28	Mixed	31.4 mo (mean)	15 (53.6)	Age range: 2-17 y
Klinkenberg et al (2012) ²⁴	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) ³⁵	Case series	24	LGS	24 mo	NR ^c	Age: <12 y
Healy et al (2013) ³⁶	Retrospective case review	16	Unknown	3-y review	9 (56)	Age: <12 y
Terra et al (2014) ³⁷	Retrospective case-control ^d	36	Mixed	3-y review	VNS group: 20 (55.4)	Age: <18 y Difference from baseline seizure frequency ^e
Yu et al (2014) ³⁸	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; SFR: seizure frequency reduction; 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-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. Food and Drug Administration 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.³⁹ 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.^{40,41} 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.^{42,43} Analyses from these study groups were presented for Food and Drug Administration 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).⁴⁴ Patients who responded to sham treatment in the short-term RCT ($\approx 10\%$) 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. 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 four 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 were some losses to follow-up.⁴⁵⁻⁴⁷ 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.^{43,44} Fifteen percent of VNS subjects responded vs 10% of control subjects ($p=0.31$). The Inventory for Depressive Symptomatology Systems Review 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.^{42,44} 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.⁴⁴ 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 might 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.⁴⁸ 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 inconclusive.^{43,44} Daban et al (2008) concluded that further clinical trials are needed to confirm efficacy of VNS in treatment-resistant depression.⁴⁸

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.⁴⁹ 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 (2013)⁵⁰ reported on 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, D-03 (Bajbouj et al [2010]⁵¹), D-04, and D-21 (Aaronson et al [2013]⁵²) study 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.

Liu et al (2014) 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 ages 65 years or older.⁵³ Reviewers identified 2 small studies that evaluated the effect of VNS on cognition in patients with Alzheimer disease, one with 10 subjects and the other with 17 subjects, which were mixed in demonstrating clinical improvements.

Aaronson et al (2013) 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).⁵² 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 were no statistically significant differences between the dose groups for the study's primary outcome, change in IDS score from baseline. However, mean IDS scores 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 might 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), which followed patients for 2 years, showed that 53.1% (26/49) met criteria for a treatment response and 38.9% (19/49) met criteria for remission.⁵¹ A small 2008 study of 9 patients with rapid-cycling bipolar disorder showed improvements in several depression rating scales over 40 weeks of observation.⁵⁴ Another case series, by Cristancho et al (2011), which followed patients for 1 year, showed that 4 of 15 responded and 1 of 15 remitted according to the principal response criteria.⁵⁵ 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.⁵⁶

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.⁴⁴

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 in 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 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.⁵⁷ The ANTHEM-HF trial (2014) is another case series, but in it, patients were randomized to right- or left-sided vagus nerve implantation (but without a control group).⁵⁸ 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).

Zannad et al (2015) 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.⁵⁹ 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 Summary 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 might 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.⁶⁰ Twenty-one subjects were randomized to VNS plus rehabilitation or rehabilitation alone. The mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group and +3.0 in the control group ($p=0.064$). Six patients in the VNS group achieved a clinically meaningful response and 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,⁶¹ fibromyalgia,⁶² headaches,^{63,64} and tinnitus.⁶⁵ The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited, but there are no RCTs.⁶⁶ None of these studies are sufficient to draw 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 draw conclusions on the effect of VNS.

Transcutaneous VNS

Only conditions for which there is at least 1 RCT assessing the use of transcutaneous VNS (t-VNS) are discussed because case series are inadequate to determine the effect of the technology.

Episodic Cluster Headaches

Goadsby et al (2017) reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of cluster headache attacks.⁶⁷ Ninety-two patients with cluster headaches were randomized to t-VNS (described in this response as noninvasive VNS) or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the t-VNS and sham treatment groups. The primary efficacy end point was the ability to achieve pain-free status within 15 minutes of initiation of treatment without use of rescue treatment. There was no difference between t-VNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between t-VNS-treated and sham-treated patients. For the episodic cluster headaches subgroup, t-VNS demonstrated a 48% response rate compared with 6% response rate for sham-treated ($p<0.01$).

Silberstein et al (2016) reported on the results of a randomized, double-blind, sham-controlled study (ACT1) of cluster headache attacks.⁶⁸ One hundred fifty patients with cluster headaches were randomized to t-VNS or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the t-VNS and sham treatment groups. The primary end point was response rate defined as the ability to achieve pain-free status within 15 minutes of initiation of treatment without rescue medication use through 60 minutes. There were no differences between t-VNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between t-VNS-treated and sham-treated patients. For the episodic cluster headache subgroup, t-VNS demonstrated a 34.2% response rate compared with 10.6% response rate for sham-treated ($p=0.008$).

Gaul et al (2016) reported on the results of a randomized open-label study of t-VNS for the treatment of chronic cluster headache.⁶⁹ Forty-eight patients with chronic cluster headache were randomized to t-VNS or 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 might have resulted in placebo response in the t-VNS group.

Subsection Summary: Transcutaneous VNS for Episodic Cluster Headaches

Transcutaneous (or noninvasive) VNS has been investigated for episodic cluster headaches in 3 RCTs. One RCT assessing cluster headache showed a reduction in headache frequency but did not have a sham treatment group. Two randomized, double-blind, sham-controlled studies (ACT1 and ACT2) showed efficacy in achieving pain-free status within 15 minutes of treatment with t-VNS. However, the ACT1 and ACT2 studies had small episodic cluster headache subgroups of 85 (38 treated, 45 sham) and 27 (14 treated, 13 sham) respectively. Additional studies with larger cohorts of patients with episodic cluster headache are required given the small sample sizes evaluated in these trials.

Other Neurologic, Psychiatric, or Metabolic Disorders

Epilepsy

Aihua et al (2014) reported on results from a series of 60 patients with pharmaco-resistant epilepsy treated with a 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.⁷⁰ 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 identified 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.⁷¹ 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 24.⁷²

Psychiatric Disorders

Hein et al (2013) reported on results of 2 pilot RCTs of a t-VNS device for the treatment of depression, one of which included 22 subjects and another assessed 15 subjects.⁷³ In the first study, 11 subjects were randomized to active or sham t-VNS. At 2-week 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 BDI scores (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 a significant change in BDI scores (28.6 to 25.4 points). The authors did not report direct comparisons in BDI change scores between the sham- and active-stimulation groups.

Hasan et al (2015) reported on a randomized trial of t-VNS for the treatment of schizophrenia.⁷⁴ Twenty patients were assigned to active t-VNS or 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.⁷⁵ 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 pharmacoresistant epilepsy (Stefan et al [2012]⁷¹; previously described). Reviewers also included a fifth study in a data table, although not in their text or a reference list (Hein et al [2013]⁷³; previously described). Overall, the studies assessed were limited by small size and poor generalizability.

Other Headaches

Goadsby et al (2014) reported on results from an open-label pilot study of t-VNS for the treatment of a migraine with or without aura.⁷⁶ 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.

Tso et al (2017) evaluated the records of 15 patients treated with a t-VNS device (gammaCore) for paroxysmal hemicrania (n=6) or hemicrania continua (n=9) as primary treatment or as an adjunct to indomethacin.⁷⁷ Symptom-related outcomes included reduction of pain severity and reduced frequency of attacks: for the first, 7 hemicrania continua patients saw improvement with t-VNS therapy, as did 3 patients with paroxysmal hemicranias. The frequency of attacks was

reduced for 2 hemicrania continua patients and 2 paroxysmal hemicranias patients. Some adverse events were reported in all patients, although not detailed.

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.⁷⁸ 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 for Other Neurologic, Psychiatric, or Metabolic Disorders
Transcutaneous VNS has been investigated in 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 than for sham controls; however, the high dropout rates in this trial are problematic. In the study of depression, a small RCT that compared treatment using t-VNS with sham stimulation demonstrated some improvements in depression scores with t-VNS; however, the lack of comparisons between groups limits conclusions that might be drawn. 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 significant reductions in seizure frequency for patients with partial-onset seizures. The uncontrolled studies have consistently reported large reductions in 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, 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 in 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 evaluating chronic heart failure 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. This pilot study has provided 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, 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 draw conclusions regarding efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Transcutaneous Vagus Nerve Stimulation

For individuals with episodic cluster headaches who receive transcutaneous VNS, the evidence includes 3 RCTs. One RCT for a cluster headache showed a reduction in headache frequency but did not include a sham treatment group. Two randomized, double-blind, sham-controlled studies showed efficacy of achieving pain-free status within 15 minutes of treatment with noninvasive VNS in patients with episodic cluster headaches but not in patients with chronic cluster headaches. The RCTs for episodic cluster headaches are promising, however, additional studies with larger relevant populations are required to establish the treatment efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have other neurologic, psychiatric, or metabolic disorders (eg, epilepsy, depression, schizophrenia, noncluster 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 patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Academy of Neurology

In 1999, the American Academy of Neurology released a consensus statement on the use of vagus nerve stimulation (VNS) in adults, which 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."⁷⁹ The Academy updated these guidelines in 2013, stating: "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)."⁸⁰ An update is reported to be in progress at the time of this review update.

American Psychiatric Association

The American Psychiatric Association guidelines for the treatment of major depressive disorder in adults, updated in 2010, included 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).⁸¹

European Headache Federation

In 2013, the European Headache Federation issued a consensus statement on neuromodulation treatments for chronic headaches, which made 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."⁸²

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02113033 ^a	Vagal Nerve Stimulation: safeGUARDing Heart Failure Patients	20	Mar 2016 (ongoing)
NCT02385526 ^a	ASCEND: Vagus Nerve Stimulation Titration Protocol to Improve Tolerance and Accelerate Adaptation	60	Apr 2017 (ongoing)
NCT02686034 ^a	A Prospective, Multi-centre, Randomized, Double-blind, Sham-controlled Study of gammaCore® Non-invasive Vagus Nerve Stimulator (nVNS), for the Acute Treatment of Migraine	300	Apr 2017 (ongoing)
NCT02378792 ^a	The Clinical Research on TsingHua Vagus Nerve Stimulator for Treatment of Refractory Epilepsy Enrollment	300	Dec 2017 (ongoing)
NCT02983448	Noninvasive Neuromodulation to Reserve Diastolic Dysfunction	26	Dec 2017 (ongoing)
NCT03062514 ^a	Vagus Nerve Stimulation for Pediatric Intractable Epilepsy (VNS-PIE)	84	Mar 2018
NCT02648191	Preoperative Treatment With Noninvasive Intra-auricular Vagus Nerve Stimulation Pending Bariatric Surgery. A Randomized, Controlled, Double-blind Trial	50	Apr 2018
NCT03380156	Effect of Transcutaneous Vagal Stimulation (TVS) on Endothelial Function and Arterial Stiffness in Patients With Heart Failure With Reduced Ejection Fraction	25	May 2018
NCT02359188	Influence of Transcutaneous Vagal Nerve Stimulation on Expression of microRNA, Cytokines, Chemokines and Neuropeptides as Well as Cerebral Resting State and Gastric Motility	60	Aug 2018
NCT01281293 ^a	A Post Market, Long Term, Observational, Multi-site Outcome Study to Follow the Clinical Course and Seizure Reduction of Patients With Refractory Seizures Who Are Being Treated With Adjunctive VNS Therapy	124	Dec 2018
NCT03163030 ^a	Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure With Preserved Ejection Fraction (ANTHEM-HFpEF) Study	50	Dec 2018
NCT03217929	Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) for Food Craving in Obese Individuals: A Randomized, Sham-controlled, Double Blind Clinical Trial	54	Oct 2019

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03282110	Comprehensive Acupuncture for Depressive Disorder With Comorbid Psychogenic Pain: Randomized Controlled Study	60	Jun 2019
NCT03327649	Neuromodulation of Inflammation to Treat Heart Failure With Preserved Ejection Fraction	72	Dec 2019
NCT03320304 ^a	A Global Prospective, Multi-center, Observational Post-market Study to Assess short, Mid and Long-term Effectiveness and Efficiency of VNS Therapy® as Adjunctive Therapy in real-world patients With difficult to Treat Depression	500	Dec 2025
Unpublished			
NCT02562703	Transcutaneous Vagus Nerve Stimulation for Treating Major Depressive Disorder: a Phase II, Randomized, Double-blind Clinical Trial	40	Jul 2016 (unknown)
NCT02089243	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 (CoRaVNSiR)	40	Jul 2017 (unknown)
NCT01958125 ^a	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	120	Jan 2015 (completed)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

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

CPT/HCPCS

- 61885 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
- 61886 Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
- 64553 Percutaneous implantation of neurostimulator electrode array; cranial nerve
- 64568 Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
- 64569 Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
- 64570 Removal of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator

- 95976 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
- 95977 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
- 95983 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
- 95984 Electronic analysis of implanted neurostimulator pulse generator/transmitter (eg, contact group(s), interleaving, amplitude, pulse width, frequency (Hz), on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional
- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
- L8685 Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
- L8686 Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
- Vagus 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. There are CPT codes that specifically describe the neurostimulator programming and analysis of cranial nerve stimulation (ie, vagus nerve) as follows: 95974, 95975.

ICD-10 Diagnoses (Effective October 1, 2015)

G40.001	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, with status epilepticus
G40.011	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, with status epilepticus
G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, without status epilepticus
G40.101	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, with status epilepticus
G40.111	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus
G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus
G40.201	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, with status epilepticus
G40.211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus
G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.311	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus
G40.319	Generalized idiopathic epilepsy and epileptic syndromes, intractable, without status epilepticus
G40.401	Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.411	Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus
G40.419	Other generalized epilepsy and epileptic syndromes, intractable, without status epilepticus
G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus
G40.801	Other epilepsy, not intractable, with status epilepticus
G40.811	Lennox-Gastaut syndrome, not intractable, with status epilepticus
G40.813	Lennox-Gastaut syndrome, intractable, with status epilepticus
G40.814	Lennox-Gastaut syndrome, intractable, without status epilepticus
G40.821	Epileptic spasms, not intractable, with status epilepticus
G40.823	Epileptic spasms, intractable, with status epilepticus
G40.824	Epileptic spasms, intractable, without status epilepticus
G40.A01	Absence epileptic syndrome, not intractable, with status epilepticus
G40.A11	Absence epileptic syndrome, intractable, with status epilepticus
G40.A19	Absence epileptic syndrome, intractable, without status epilepticus
G40.B01	Juvenile myoclonic epilepsy, not intractable, with status epilepticus
G40.B11	Juvenile myoclonic epilepsy, intractable, with status epilepticus
G40.B19	Juvenile myoclonic epilepsy, intractable, without status epilepticus

REVISIONS	
10-08-2008	<p>Revised title from Vagal Nerve Stimulator to Vagus Nerve Stimulation</p> <p>Added Rationale section</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added L8689 <p>Added Revisions section</p>
10-26-2010	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Policy language liberalized from: <p>"Vagal nerve stimulation is medically necessary for:</p> <ol style="list-style-type: none"> 1. Patient not responding to anticonvulsant medications with multiple medications tried 2. Patient not a candidate for a surgical procedure 3. Medically refractory seizures (i.e. Lennox-Gastaut) in children under 12 years" to: "A. Vagus nerve stimulation may be considered medically necessary as a treatment of medically refractory seizures. <ul style="list-style-type: none"> ▪ Policy language liberalized from: <p>"Vagal nerve stimulation is experimental / investigational because effectiveness has not been established for all other indications including:</p> <ol style="list-style-type: none"> 1. Autism, 2. Obesity, 3. Refractory depression, 4. Obsessive-compulsive disorder, 5. Cognitive impairment associated with Alzheimer's disease, and 6. Depression" <p>to: "B. Vagus nerve stimulation is considered experimental / investigational as a treatment of other conditions." with the reference to indications being removed as the list was not all inclusive.</p> <p>Added Policy Guidelines section and the following wording:</p> <ul style="list-style-type: none"> ▪ "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." <p>Updated Rationale section</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated wording for CPT/HCPCS codes: 61886, L8681, L8689 <p>Updated References section</p>
03-03-2011	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT codes: 64568, 64569, 64570 <p>Rationale section updated.</p> <p>Reference section updated.</p>
01-01-2012	<p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Revised CPT nomenclature for the following code: 64553 ▪ Removed CPT code: 64573 ▪ Removed the following CPT guidelines: <p>95974: Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance, and patient compliance measurements); complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour.</p> <p>95975: complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, each additional 30 minutes."</p>

REVISIONS	
	<ul style="list-style-type: none"> ▪ Added the following CPT guidelines: "95974: use modifier 52, if less than 31 minutes in duration."
08-24-2012	<p>Description section updated.</p> <p>In the Policy section:</p> <ul style="list-style-type: none"> ▪ In Item B, added "including, but not limited to heart failure, fibromyalgia, depression, essential tremor, obesity, and headaches." to read "Vagus nerve stimulation is considered experimental / investigational as a treatment of other conditions, including, but not limited to heart failure, fibromyalgia, depression, essential tremor, obesity, and headaches." <p>Rationale section updated.</p> <p>Reference section updated.</p>
06-26-2013	<p>Rational section updated.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 Diagnoses (<i>Effective October 1, 2014</i>)
11-24-2015	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item B removed "and" and added "tinnitus, and traumatic brain injury" to read, "Vagus nerve stimulation is considered experimental / investigational as a treatment of other conditions, including but not limited to heart failure, fibromyalgia, depression, essential tremor, obesity, headaches, tinnitus, and traumatic brain injury." <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated Coding notations. <p>References updated</p>
04-25-2016	<p>Description section updated</p> <p>Rationale section updated</p> <p>References updated</p>
12-21-2017	<p>Policy published 11-21-2017. Policy effective 12-21-2017.</p> <p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item B added "upper-limb impairment due to stroke" and removed "obesity" to read "Vagus nerve stimulation is considered experimental / investigational as a treatment of other conditions, including but not limited to depression, heart failure, upper-limb impairment due to stroke, essential tremor, headaches, fibromyalgia, tinnitus, and traumatic brain injury." ▪ In Item C added "Transcutaneous" to read "Transcutaneous (nonimplantable) vagus nerve stimulation devices are considered experimental / investigational for all indications." <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Deleted ICD -10 Codes: G40.009, G40.109, G40.209, G40.309, G40.409, G40.509, G40.802, G40.812, G40.822, G40.A09, G40.B09 <p>References updated</p>
05-09-2018	<p>Description section updated</p> <p>Rationale section updated</p> <p>References updated</p>
01-01-2019	<p>In Coding section:</p> <p>Added CPT Codes: 95976, 95977, 95983, 95984</p> <p>Removed CPT Codes: 95974, 95975</p>

REFERENCES

1. Food and Drug Administration. Premarket Application Approval: VNS Therapy System (P970003/S207). 2017; https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s207b.pdf. Accessed January 25, 2018.
2. Food and Drug Administration. Class 2 Device Recall Model 106 AspireSR Generators (P970003S173). 2017; <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm?id=157567>. Accessed January 25, 2018.
3. Food and Drug Administration. 510(k) premarket notification: gammaCore-S (K171306). 2017; https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171306.pdf. Accessed January 25, 2018.
4. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg*. Dec 2011;115(6):1248-1255. PMID 21838505
5. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia*. May-Jun 1994;35(3):616-626. PMID 8026408
6. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. Jul 1998;51(1):48-55. PMID 9674777
7. Amar AP, Heck CN, Levy ML, et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. *Neurosurgery*. Dec 1998;43(6):1265-1276; discussion 1276-1280. PMID 9848840
8. Scherrmann J, Hoppe C, Kral T, et al. Vagus nerve stimulation: clinical experience in a large patient series. *J Clin Neurophysiol*. Sep 2001;18(5):408-414. PMID 11709645
9. DeGiorgio C, Heck C, Bunch S, et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. *Neurology*. Jul 26 2005;65(2):317-319. PMID 16043810
10. Ben-Menachem E, Hellstrom K, Waldton C, et al. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology*. Apr 12 1999;52(6):1265-1267. PMID 10214754
11. Parker AP, Polkey CE, Binnie CD, et al. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics*. Apr 1999;103(4 Pt 1):778-782. PMID 10103302
12. Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group. *Neurology*. Apr 22 1999;52(7):1510-1512. PMID 10227649
13. DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia*. Sep 2000;41(9):1195-1200. PMID 10999559
14. Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy Behav*. Jun 2003;4(3):302-309. PMID 12791333
15. Vonck K, Boon P, D'Have M, et al. Long-term results of vagus nerve stimulation in refractory epilepsy. *Seizure*. Sep 1999;8(6):328-334. PMID 10512772
16. Vonck K, Thadani V, Gilbert K, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol*. Jul-Aug 2004;21(4):283-289. PMID 15509917
17. Majoie HJ, Berfelo MW, Aldenkamp AP, et al. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: clinical results, neuropsychological effects, and cost-effectiveness. *J Clin Neurophysiol*. Sep 2001;18(5):419-428. PMID 11709647
18. Majoie HJ, Berfelo MW, Aldenkamp AP, et al. Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. *Seizure*. Jan 2005;14(1):10-18. PMID 15642494
19. Huf RL, Mamelak A, Kneedy-Cayem K. Vagus nerve stimulation therapy: 2-year prospective open-label study of 40 subjects with refractory epilepsy and low IQ who are living in long-term care facilities. *Epilepsy Behav*. May 2005;6(3):417-423. PMID 15820352
20. Kang HC, Hwang YS, Kim DS, et al. Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study. *Acta Neurochir Suppl*. Mar 2006;99:93-96. PMID 17370772
21. Ardesch JJ, Buschman HP, Wagener-Schimmel LJ, et al. Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study. *Seizure*. Oct 2007;16(7):579-585. PMID 17543546
22. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Chronic vagus nerve stimulation for treatment of seizures. *TEC Assessments*. 1998;Volume 13:Tab 9. PMID

23. Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. *Cochrane Database Syst Rev*. Apr 03 2015(4):Cd002896. PMID 25835947
24. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol*. Sep 2012;54(9):855-861. PMID 22540141
25. Michael JE, Wegener K, Barnes DW. Vagus nerve stimulation for intractable seizures: one year follow-up. *J Neurosci Nurs*. Dec 1993;25(6):362-366. PMID 8106830
26. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology*. Feb 1995;45(2):224-230. PMID 7854516
27. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia*. Jun 2014;55(6):893-900. PMID 24754318
28. Englot DJ, Rolston JD, Wright CW, et al. Rates and predictors of seizure freedom with vagus nerve stimulation for intractable epilepsy. *Neurosurgery*. Sep 2016;79(3):345-353. PMID 26645965
29. Garcia-Navarrete E, Torres CV, Gallego I, et al. Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication. *Seizure*. Jan 2013;22(1):9-13. PMID 23041031
30. Hornig GW, Murphy JV, Schallert G, et al. Left vagus nerve stimulation in children with refractory epilepsy: an update. *South Med J*. May 1997;90(5):484-488. PMID 9160063
31. Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *J Pediatr*. May 1999;134(5):563-566. PMID 10228290
32. Patwardhan RV, Stong B, Bebin EM, et al. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. *Neurosurgery*. Dec 2000;47(6):1353-1357; discussion 1357-1358. PMID 11126906
33. Frost M, Gates J, Helmers SL, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *Epilepsia*. Sep 2001;42(9):1148-1152. PMID 11580762
34. You SJ, Kang HC, Kim HD, et al. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience. *J Korean Med Sci*. Jun 2007;22(3):442-445. PMID 17596651
35. Cukiert A, Cukiert CM, Burattini JA, et al. A prospective long-term study on the outcome after vagus nerve stimulation at maximally tolerated current intensity in a cohort of children with refractory secondary generalized epilepsy. *Neuromodulation*. Nov 2013;16(6):551-556. PMID 23738578
36. Healy S, Lang J, Te Water Naude J, et al. Vagal nerve stimulation in children under 12 years old with medically intractable epilepsy. *Childs Nerv Syst*. Nov 2013;29(11):2095-2099. PMID 23681311
37. Terra VC, Furlanetti LL, Nunes AA, et al. Vagus nerve stimulation in pediatric patients: Is it really worthwhile? *Epilepsy Behav*. Feb 2014;31:329-333. PMID 24210463
38. Yu C, Ramgopal S, Libenson M, et al. Outcomes of vagal nerve stimulation in a pediatric population: A single center experience. *Seizure*. Feb 2014;23(2):105-111. PMID 24309238
39. Elger G, Hoppe C, Falkai P, et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res*. Dec 2000;42(2-3):203-210. PMID 11074193
40. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Vagus nerve stimulation for treatment-resistant depression. *TEC Assessments*. 2005;Volume 21:Tab 7.
41. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Vagus nerve stimulation for treatment-resistant depression. *TEC Assessments*. 2006;Volume 21:Tab 7.
42. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. Sep 01 2005;58(5):364-373. PMID 16139582
43. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. Sep 1 2005;58(5):347-354. PMID 16139580
44. Food and Drug Administration. Summary of Safety and Effectiveness Data: VNS Therapy™ System. 2005; https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s050b.pdf. Accessed March 14, 2018.

45. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry*. Feb 15 2002;51(4):280-287. PMID 11958778
46. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry*. Feb 15 2000;47(4):276-286. PMID 10686262
47. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. Nov 2001;25(5):713-728. PMID 11682255
48. Daban C, Martinez-Aran A, Cruz N, et al. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. *J Affect Disord*. Sep 2008;110(1-2):1-15. PMID 18374988
49. Martin JL, Martin-Sanchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. *Eur Psychiatry*. Apr 2012;27(3):147-155. PMID 22137776
50. Berry SM, Broglio K, Bunker M, et al. A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. *Med Devices (Auckl)*. Mar 2013;6:17-35. PMID 23482508
51. Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *J Clin Psychopharmacol*. Jun 2010;30(3):273-281. PMID 20473062
52. Aaronson ST, Carpenter LL, Conway CR, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimul*. Jul 2013;6(4):631-640. PMID 23122916
53. Liu AY, Rajji TK, Blumberger DM, et al. Brain stimulation in the treatment of late-life severe mental illness other than unipolar nonpsychotic depression. *Am J Geriatr Psychiatry*. Mar 2014;22(3):216-240. PMID 23891366
54. Marangell LB, Suppes T, Zboyan HA, et al. A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry*. Feb 2008;69(2):183-189. PMID 18211128
55. Cristancho P, Cristancho MA, Baltuch GH, et al. Effectiveness and safety of vagus nerve stimulation for severe treatment-resistant major depression in clinical practice after FDA approval: outcomes at 1 year. *J Clin Psychiatry*. Oct 2011;72(10):1376-1382. PMID 21295002
56. Tisi G, Franzini A, Messina G, et al. Vagus nerve stimulation therapy in treatment-resistant depression: a series report. *Psychiatry Clin Neurosci*. Aug 2014;68(8):606-611. PMID 25215365
57. De Ferrari GM, Crijns HJ, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J*. Apr 2011;32(7):847-855. PMID 21030409
58. Premchand RK, Sharma K, Mittal S, et al. autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail*. Nov 2014;20(11):808-816. PMID 25187002
59. Zannad F, De Ferrari GM, Tuinenburg AE, et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. *Eur Heart J*. Feb 14 2015;36(7):425-433. PMID 25176942
60. Dawson J, Pierce D, Dixit A, et al. Safety, feasibility, and efficacy of vagus nerve stimulation paired with upper-limb rehabilitation after ischemic stroke. *Stroke*. Jan 2016;47(1):143-150. PMID 26645257
61. Handforth A, Ondo WG, Tatter S, et al. Vagus nerve stimulation for essential tremor: a pilot efficacy and safety trial. *Neurology*. Nov 25 2003;61(10):1401-1405. PMID 14638963
62. Lange G, Janal MN, Maniker A, et al. Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. *Pain Med*. Sep 2011;12(9):1406-1413. PMID 21812908
63. Mauskop A. Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. *Cephalalgia*. Feb 2005;25(2):82-86. PMID 15658944
64. Cecchini AP, Mea E, Tullo V, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. *Neurol Sci*. May 2009;30(Suppl 1):S101-104. PMID 19415436

65. De Ridder D, Vanneste S, Engineer ND, et al. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. *Neuromodulation*. Feb 2014;17(2):170-179. PMID 24255953
66. Engineer CT, Hays SA, Kilgard MP. Vagus nerve stimulation as a potential adjuvant to behavioral therapy for autism and other neurodevelopmental disorders. *J Neurodev Disord*. Jul 2017;9:20. PMID 28690686
67. Goadsby PJ, de Coo IF, Silver N, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia*. Jan 1 2017;333102417744362. PMID 29231763
68. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-invasive vagus nerve stimulation for the ACute Treatment of Cluster Headache: findings from the randomized, double-blind, sham-controlled ACT1 Study. *Headache*. Sep 2016;56(8):1317-1332. PMID 27593728
69. Gaul C, Diener HC, Silver N, et al. Non-invasive vagus nerve stimulation for PREvention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study. *Cephalalgia*. May 2016;36(6):534-546. PMID 26391457
70. Aihua L, Lu S, Liping L, et al. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. *Epilepsy Behav*. Oct 2014;39:105-110. PMID 25240121
71. Stefan H, Kreiselmeier G, Kerling F, et al. Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. *Epilepsia*. Jul 2012;53(7):e115-118. PMID 22554199
72. He W, Jing X, Wang X, et al. Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: a pilot trial. *Epilepsy Behav*. Sep 2013;28(3):343-346. PMID 23820114
73. Hein E, Nowak M, Kiess O, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. *J Neural Transm*. May 2013;120(5):821-827. PMID 23117749
74. Hasan A, Wolff-Menzler C, Pfeiffer S, et al. Transcutaneous noninvasive vagus nerve stimulation (tVNS) in the treatment of schizophrenia: a bicentric randomized controlled pilot study. *Eur Arch Psychiatry Clin Neurosci*. Oct 2015;265(7):589-600. PMID 26210303
75. Shiozawa P, Silva ME, Carvalho TC, et al. Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: a systematic review. *Arq Neuropsiquiatr*. Jul 2014;72(7):542-547. PMID 25054988
76. Goadsby PJ, Grosberg BM, Mauskop A, et al. Effect of noninvasive vagus nerve stimulation on acute migraine: an open-label pilot study. *Cephalalgia*. Oct 2014;34(12):986-993. PMID 24607501
77. Tso AR, Marin J, Goadsby PJ. Noninvasive vagus nerve stimulation for treatment of indomethacin-sensitive headaches. *JAMA Neurol*. Oct 1 2017;74(10):1266-1267. PMID 28846758
78. Huang F, Dong J, Kong J, et al. Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: a pilot randomized study. *BMC Complement Altern Med*. Jun 26 2014;14:203. PMID 24968966
79. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. Sep 11 1999;53(4):666-669. PMID 10489023
80. Morris GL, 3rd, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. Oct 15 2013;81(16):1453-1459. PMID 23986299
81. American Psychiatric Association, Work Group on Major Depressive Disorder, Gelenberg Aj, et al. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. Third Edition. 2010; 3rd ed.:http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed January 25, 2018.
82. Martelletti P, Jensen RH, Antal A, et al. Neuromodulation of chronic headaches: position statement from the European Headache Federation. *J Headache Pain*. Oct 21 2013;14(1):86. PMID 24144382

83. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for VAGUS Nerve Stimulation (VNS) (160.18). 2007; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=230&ncdver=2&CoverageSelection=National&Keyword=vagus&KeywordLookUp=Title&KeywordSearchType=And&where=%252520index&nca_id=%252520195&bc=gAAAABAAAAAAA%3d%3d&. Accessed January 25, 2018.

Other References:

1. Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee, June 2006.
2. Blue Cross and Blue Shield of Kansas Behavioral Health Liaison Committee, June 2007.