Medical Policy

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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 chronic cluster headache	Interventions of interest are: • Transcutaneous vagus nerve stimulation with standard of care to prevent cluster headaches	Comparators of interest are: • Standard of care: medication to prevent cluster headaches	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • with cluster headache	Interventions of interest are: • Transcutaneous vagus nerve stimulation to treat acute cluster headache	Comparators or interest are: • Standard of care to treat acute migraine headache	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Functional outcomes
Individuals: • with migraine headache	Interventions of interest are: • Transcutaneous vagus nerve stimulation to treat acute migraine headache	Comparators or interest are: • Standard of care to treat acute migraine headache	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • 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 include 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.

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

Regulatory Status

Table 1 includes updates on FDA approval and clearance for VNS stimulators devices pertinent to this evidence review.

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

Device Name	Manufacturer	Cleared	PMA/510(k)	Product Code(s)	Indications
NeuroCybernetic Prosthesis (NCP®)	LIvaNov (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

Device Name	Manufacturer	Cleared	PMA/510(k)	Product Code(s)	Indications
		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/ 2018	DEN150048/ K171306/ K173442	PKR, QAK	Indicated for acute treatment of pain associated with episodic cluster and migraine headache in adults using noninvasive VNS on the side of the neck
gammaCore-2®,gammaCore-Sapphire®	ElectroCore	2017/ 2018	K172270/ K180538/ K182369	PKR	Indicated for: Adjunctive use for the preventive treatment of cluster headache in adult patients. The acute treatment of pain associated with episodic cluster headache in adult patients. The acute treatment of pain associated with migraine headache in adult patients.

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 despite 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 4, 2018.

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 1) patients with medically refractory seizures; 2) treatment-resistant depression; 3) other conditions (e.g., chronic heart failure, upper-limb impairment due to stroke, essential tremor, fibromyalgia, tinnitus, and autism)

Interventions

The test being considered is implantable VNS.

Surgically implanted VNS devices 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.

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

For treatment of refractory epilepsy, the following practices are currently being used: resective surgery, additional trials of conventional antiepileptic drugs and/or a ketogenic diet.

For treatment-resistant depression, additional therapy such as adding a different class of medication or adding psychotherapy, switching to a different therapy such as a different antidepressant or electroconvulsive therapy are practices that may be used.

Outcomes
For treatment of refractory epilepsy, the outcomes of interest are seizure frequency and severity, reduction in seizure frequency by >50%, quality of life and functional outcomes, cognitive function, mediation use and treatment-related morbidity.

For treatment-resistant depression, the outcomes of interest are depression symptoms as measured by the Montgomery-Asberg Depression Rating Scale or Hamilton Depression Rating Scale, response and remission global impression of change, suicide, quality of life and functional outcomes, and treatment-related morbidity. Relief of depression symptoms can 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)

Timing
For treatment-resistant depression, data on outcomes related to depression symptoms are needed over the short term (2 to 6 months) and the long-term (1 to 2 years).

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs or systematic reviews ofRCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies or systematic reviews of prospective studies.

c. To assess longer term outcomes and adverse events, single-arm studies or systematic reviews of single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

Treatment-Resistant Seizures

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. Characteristics of systematic reviews are shown in Table 2. Results are shown in Tables 3 and 4.

Panebianco et al (2015) updated a Cochrane systematic review and meta-analysis of VNS to treat partial seizures.[1,] 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. Results are shown in Table 3. RIsk of bias was rated as low for most domains across studies. However, none of the protocols for the included studies were available and therefore were rated as having an unclear risk of bias for selective reporting. In addition, all studies were sponsored by the manufacturers of the device.

Table 2. Characteristics of Systematic Reviews of implantable VNS for epilepsy

Study	Dates	Studies	Participants	N (Range)	Design	Duration
Panebianco (2015)	Up to 2015	5	Adults or children with drug-resistant partial seizures not eligible for surgery or who failed surgery	439 (22 to 198)	RCT	12 to 20 weeks
Englot (2011)	Up to 2010	15	Adults or children with medically refractory epilepsy	955 (16 to 196)	RCT or prospective observational study	3 months to 5 years

Table 3. Results of Systematic Reviews of RCTs of implantable VNS for epilepsy

Study	50% or greater reduction in seizure frequency	VNS Treatment withdrawal	Voice Alteration or Cough	Cough	Dyspnea
Panebianco (2015)					
Total N	373	375	334	334	312
Pooled effect (95% CI)	1.73 (1.13 to 2.64)	2.56 (0.51 to 12.71)	2.17 (1.49 to 3.17)	1.09 (0.74 to 1.62)	2.45 (1.07 to 5.60)
I^2 (p^1)	18% (p=0.30)	0% (p=0.74)	32% (p=0.23)	0% (p=0.54)	0% (p=0.77)

1p for heterogeneity

Englot et al (2011) conducted a systematic review of the literature through November 2010 assessing the efficacy of VNS and its predictors of response.[2,] Fifteen RCTs and prospective observational studies were included. Analyses combined different study types. Given that the meta-analysis of RCTs is described in the Cochrane review, the observational studies only from the Englot review are shown in Table 4.

Table 4. Summary of Prospective Studies Included in Englot (2011) Systematic Review

Study (year)	N	Duration of FU	No. of sites	Seizure Type	Seizure Frequency Reduction >50%, %
Ben-Menachem et al (1999)[3,]	64	3-64 mo	Single	Mixed	45
Parker et al (1999)[4,]	15a	1 y	Single	Mixed	27
Labar et al (1999)[5,]	24	3 mo	Single	Generalized	46
DeGiorgio et al (2000)[6,]	195	12 mo	Multisite	Mixed	35
Chavel et al (2003)[7,]	29	1-2 y	Single	Partial	54b
Vonck et al (1999[8,] ; 2004[9,])	118	> 6 mo	Multisite	Mixed	50
Majoie et al (2001[10,] ; 2005[11,])	19a	2 y	Single	Mixed	21
Huf et al (2005)[12,]	40c	2 y	Single	NR	28
Kang et al (2006)[13,]	16d	>1 y	Multisite	Mixed	50
Ardesch et al (2007)[14,]	19	>2 y	Single	Partial	33e

Adapted from Englot et al (2011).[2,] FU: follow-up; NR: not reported: OBS: observational; .a Children with encephalopathy. b Rate at 1-year follow-up. c Adults with low IQ. d Children. e Rate at 2 years.

Randomized Controlled Trials

As noted in the previous section, five RCTs (n=439 participants) have evaluated VNS. Four trials compared high frequency VNS that was thought to be therapeutic versus low frequency VNS at levels that were thought to be sub-therapeutic. One trial compared rapid versus medium versus slow cycle VNS. Characteristics of the trials are shown below in Table 5. Results are shown in Table 6.

Table 5. Characteristics of Double-blind RCTs of VNS for epilepsy

Study; Trial	Countries/single or multi-center	Dates	Participants	Interventions	
				Active	Comparator
Michael (1993)[15,]	US (multicenter)	NR	Patients with refractory partial seizures	N=10 High stimulation	N=12 Low stimulation
Ben-Menchem/VNS Study Group (1994, 1995)[16,3,]	USA, Canada, Sweden and Germany (multicenter)	~1991	Patients with refractory partial (simple or complex) seizures Mean age, 35 years (range 14 to 57)	N=54 High stimulation	N=60 Low stimulation
Handforth (1998)[17,]	US (multicenter)	1995 to 1996	Patients with 6+ partial-onset seizures over 30 days including complex partial or secondarily generalized seizures	N=95 High stimulation	N=103 Low stimulation
DeGiorgio (2005)[18,]	US (multicenter)	NR	Patients ages 12 years and older, one or more antiepileptic medications and at least one seizure/30 days with alteration of consciousness	N=19 Rapid cycle N=19 med cycle	N=23 slow cycle
Klinkenberg (2012)[19,]	Holland (multicenter)	NR	Children with medically refractory epilepsy not eligible for epilepsy surgery	N=21 High output	N=20 Low output

The trials generally included people with drug resistant partial epilepsy with VNS as an add-on treatment. The blinded treatment phase ranged from 12 to 20 weeks in the five trials. Four trials reported the outcome of response (50% or greater reduction in seizure frequency) and the risk ratio for ranged from 1.49 to 8.27 in the 3 trials that favored high frequency VNS; the risk ratio

was statistically significantly different from the null in one trial. One trial reported a risk ratio that did not favor high frequency VNS for the response outcome but was not statistically significant.

Table 6. Results of Double-blind RCTs of VNS for epilepsy

Study	50% or greater reduction in seizure frequency (%)	Change in Seizure Frequency	Quality of life	Functional Outcomes
Michael (1993)				
N	22	NR	NR	NR
High stimulation	30%			
Low stimulation	0%			
Treatment effect (95% CI)	RR=8.27 (0.48 to 143.35)			
Ben-Menchem/VNS Study Group (1994, 1995)				
N	114	67	NR	NR
High stimulation	31%	-31%		
Low stimulation	13%	-11%		
Treatment effect(95% CI)	RR=2.36 (1.11 to 5.03)	Difference=-20% (NR); p=0.03		
Handforth (1998)			Global evaluation scores of patient well-being with visual analog scale by blinded interviewer at visits 7-9, mean	
N	196	196	NR	
High stimulation	23%	-28%	NR	
Low stimulation	16%	-15%	NR	
Treatment effect(95% CI)	RR=1.49 (0.84 to 2.66)	p=0.04	Difference=4.0 mm (0.6 to 7.4); p=0.02	
DeGiorgio (2005)		Median % reduction at 3 months		
N	42	NR	NR	NR
Rapid cycle	32%	-26%		
Slow cycle	26%	-29%		
Treatment effect(95% CI)	NR	NR		
Klinkenberg (2012)				
N	41	41	NR	NR
High stimulation	14%	+23%		
Low stimulation	20%	-9%		
Treatment effect(95% CI)	RR=0.71 (0.18 to 2.80)	p=0.61		

RR=Risk ratio; NR=not reported

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.[20,]

Observational studies

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.[21,] 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 7. These rates did not differ statistically from participants with predominantly partial seizures.

Table 7. 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	≈60b	≈9a

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.[22,] 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.

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

Table 8. 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)[23],	Case series	19	Mixed	2-30 mo	10 (53)	Prior failed resective surgery: n=3
Murphy et al (1999)[24],	Prospective OBS	60	Mixed	18 mo	46 (42)a	Age: 26% <12 y
Patwardhan et al (2000)[25],	Case series	38	Mixed	12 mo (median)	26 (68)	Age: 11 mo to 16 y
Frost et al (2001)[26],	Retrospective case review	50	LGS	6 mo	50 (57.9)a	Age: 13 y (median)
You et al (2007)[27],	Prospective OBS	28	Mixed	31.4 mo (mean)	15 (53.6)	Age range: 2-17 y
Klinkenberg et al (2012)[19],	RCTb	41	Mixed	19 wk	High-stim: 3/21(14.2)Low-stim: 4/20 (20)	Age range: 3-17 y
Cukiert et al (2013)[28],	Case series	24	LGS	24 mo	NRc	Age: <12 y
Healy et al (2013)[29],	Retrospective case review	16	Unknown	3-y review	9 (56)	Age: <12 y
Terra et al (2014)[30],	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)[31],	Retrospective case review	69/252f	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 RCTs meta-analyses, and numerous uncontrolled studies. RCTs and meta-analyses of RCTs have 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

Systematic Reviews

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 one randomized trial.[32,] VNS was found to be associated with a reduction in depressive symptoms in the open-label studies. However, results from the only double-blind trial were considered inconclusive.[33,34,] Daban et al (2008) concluded that further clinical trials are needed to confirm efficacy of VNS in treatment-resistant depression.[32,]

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)[49,] 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][49,]), D-04, and D-21 (Aaronson et al [2013][49,]) 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.

Randomized controlled trials

One 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.[33, 34,]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).

Rush et al (2005) reported results of a 10-week, blinded RCT comparing adjunctive VNS with sham in 235 outpatients with nonpsychotic major depressive disorder or nonpsychotic, depressed phase, bipolar disorder.[33,]The patients were treatment resistant defined as those who had not responded adequately to between two and six research-qualified medication trials for the current episode of depression. The primary outcome was response rates (50% or more reduction from baseline on the Hamilton Rating Scale for Depression. There was not a statistically significant difference in response rates at 10 weeks in VNS versus sham (15% vs 10%; p=0.25).

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).[49,] 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.

Prospective Observational Studies

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.[49,34,] 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.

Case series

Several case series published before the randomized trials 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.[49,44,49,] Natural history, placebo effects, and patient and provider expectations make it difficult to infer efficacy from case series data.

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.[49,] A small 2008 study of 9 patients with rapid-cycling bipolar disorder showed improvements in several depression rating scales over 40 weeks of observation.[44,] 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.[49,]

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.[34,]

Section Summary: Treatment-Resistant Depression
There is an are two RCTs evaluating the efficacy of implanted VNS for treatment-resistant depression compared to sham and one RCT comparing therapeutic to low-dose implanted VNS. The sham-controlled trials reported only short-term results and found no significant improvement in the primary outcome with VNS. The low-dose VNS controlled trial reported no statistically significant differences between the dose groups for change in depression symptom score from baseline. 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.[44,] 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).[49,] 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.[49,] 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.[49,] 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,[49,] fibromyalgia,[49,]and tinnitus.[50,] The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited, but there are no RCTs.[51,] 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.

NONINVASIVE VAGUS NERVE STIMULATION

Clinical Context and Test Purpose

The purpose of noninvasive or transcutaneous vagus nerve stimulation (nVNS or tVNS) is to non-invasively apply low-voltage electrical currents to stimulate the cervical branch of the vagus nerve. nVNS has been tested primarily in the setting of headache. nVNS has been proposed as an intervention to relieve pain in acute attacks of cluster or migraine headaches as an alternative to standard care and to reduce the frequency of attacks for both cluster headaches and migraine as an adjunct to standard care. Proposed uses have been tested in other neurologic, psychiatric, or metabolic disorders as well.

The question addressed in this evidence review is this: Does the use of nVNS as a treatment for cluster headache, migraine or other neurologic, psychiatric, or metabolic disorders result in 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 cluster headache or migraine. The International Headache Society's International Classification of Headache Disorders classifies types of primary and secondary headaches.[52,] A summary of cluster and migraine headache based on ICHD criteria are below.

Cluster headaches are primary headaches classified as trigeminal autonomic cephalalgias that can be either episodic or chronic. The diagnostic criteria for cluster headaches[52,] states that these are attacks of severe, unilateral orbital, supraorbital, and/or temporal pain that lasts 15-180 minutes and occurs from once every other day to eight times a day and further requires for the patient to have had at least five such attacks with at least one of the following symptoms or signs, ipsilateral to the headache: conjunctival injection and/or lacrimation; nasal congestion and/or rhinorrhoea; eyelid oedema; forehead and facial sweating; miosis and/or ptosis, or; a sense of restlessness or agitation. The diagnostic criteria for episodic cluster headache requires at least two cluster periods lasting from 7 days to 1 year if untreated, and separated by pain-free remission periods of ≥3 months. The diagnostic criteria for chronic cluster headache requires

cluster headaches occurring for one year or more without remission, or with remission of less than 3 months. The age at onset for cluster headaches is generally 20-40 years and men are affected three times more often than are women.

Migraines are primary headaches that can occur with or without aura. Migraines without aura meet the following diagnostic criteria[52,]: at least five attacks lasting 4 to 72 hours if untreated or unsuccessfully treated and with at least two of the following four features: unilateral location; pulsating quality; moderate or severe pain; aggravation by or causing avoidance of routine physical activity, and having either nausea and/or vomiting and/or photophobia and phonophobia during the headache. The diagnostic criteria for migraine with aura requires two attacks with fully reversible visual, sensory, speech and/or language, motor, brainstem and/or retinal aura symptoms and at least 3 of the following: one or more aura symptoms spread gradually over ≥5 minutes; two or more aura symptoms in succession; each individual aura symptom lasts 5-60 minutes; one or more aura symptoms are unilateral; one or more aura symptoms are positive; the aura is accompanied, or followed within 60 minutes, by headache. Migraines are most common in ages 30 to 39 and women are more frequently affected than men.

Interventions
The test being considered is transcutaneous VNS as an alterative to standard care for acute headache or as an adjunct to standard care for prevention of headache.

Noninvasive devices that transcutaneously stimulate the vagus nerve on the side of the neck have been developed. The patient administers nVNS using a handheld device by placing the device on the side of the neck, over the cervical branch of the vagus nerve and positioning the metal stimulation surfaces in front of the sternocleido-mastoid muscle, over the carotid artery. The frequency and timing of stimulation vary depending on the indication. nVNS can be used multiple times a day.

Comparators
The standard of care (SOC) treatment to stop or prevent attacks of cluster headache or migraine is medical therapy. Guideline-recommended treatments for acute cluster headache attacks include oxygen inhalation and triptans (e.g., sumatriptan and zolmitriptan). Oxygen is preferred first-line, if available, because there are no documented adverse effects for most adults. Triptans have been associated with primarily nonserious adverse events; some patients experience nonischemic chest pain and distal paresthesia. Use of oxygen may be limited by practical considerations and the FDA-approved labeling for subcutaneous sumatriptan limits use to 2 doses per day. Steroids injections may be used to prevent or reduce the frequency of cluster headaches. Verapamil is also frequently used for prophylaxis although the best evidence supporting its effectiveness is a placebo-controlled RCT including 30 patients.

SOC treatments for acute migraine attacks include analgesics and/or triptans. Antiemetics and ergots may be used as monotherapy or as an adjunct for treatment of acute migraine. Beta-blockers (e.g., Metoprolol, propranolol, or timolol), antidepressants (e.g., amitriptyline orvenlafaxine) and anticonvulsants (topiramate or sodium valproate) may be used to prevent or reduce the frequency of migraine attacks along with lifestyle measures. Choosing which preventive medical therapy to use depends on patient characteristics

and comorbid conditions, medication adverse events, and patient preference. Calcitonin gene-related peptide (CGRP) antagonists have also been approved for migraine prevention.

Given the high placebo response rate in both cluster and migraine headache, trials with sham nVNS are most relevant.

Outcomes
The general outcomes of interest are headache intensity and frequency, the effect on function and quality of life and adverse events.

The most common outcome measures for treatment of acute cluster or migraine headache are headache relief measured as a proportion of patients with reduction on a pain relief scale by a specified time (usually 15, 30, 60 or 120 minutes after administration), proportion of patients who are pain-free by a specified time, sustaining reduction or pain-free for 24 hours, time to reduction or pain-free, and use of rescue medication. International Headache Society (IHS) guidelines for RCTs of drugs for migraine recommends the proportion of patients with pain score of zero (pain-free) at 2 hours before rescue medication as the primary efficacy measure in RCTs with earlier time points also being considered.[53,] IHS guidelines also state that sustained pain freedom or relapse and recurrence within 48 hours is an important efficacy outcome and that standardized, validated tools to assess the changes in ability to function and quality of life should be secondary outcomes.

The most common outcome measures for prevention of cluster or migraine headache are decrease in headache days per month compared with baseline and the proportion of responders to the treatment, defined as those patients who report more than a 50%, 75% or 100% decrease in headache days per month compared to pre-treatment.

Timing
The effect of treatment on stopping acute headache should be measured over 15 minutes to 48 hours. Continued response may be measured over many months.

The IHC guidelines suggest that effect of treatment on preventing migraine headache should be measured over at least 3 months.

Setting
The setting is outpatient care by a specialist in headache (eg neurologist).

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs or systematic reviews of RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies or systematic reviews of prospective studies.
c. To assess longer term outcomes and adverse events, single-arm studies or systematic reviews of single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

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
Randomized Controlled Trials
One RCT has evaluated nVNS for prevention of cluster headache compared to standard care and two RCTs have evaluated nNVS for treatment of acute cluster headache compared to sham nNVS. Treatment periods ranged from 2 weeks to 1 month. Characteristics of the trials are shown in Table 9. Results are shown in Table 10.

Table 9. Characteristics of RCTs of nNVS for Prevention and Treatment of Cluster Headache

						Interventions	
Author (year); Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Randomized treatment period**	**Active**	**Comparator**
PREVENTION							
Gaul (2016, 2017)[54,55]; PREVA	Germany, UK, Belgium, Italy	10	2012 to 2014	18 to 70 years of age, cCH diagnosis	4 weeks	n=48; nVNS + SO	n=49; SOC
TREATMENT							
Silberstein (2016)[56]; ACT1	US	20	2013 to 2014	18 to 75 years of age, eCH or cCH diagnosis	Up to 1 month	n=73; nVNS	n=77; Sham
Goadsby (2018)[57]; ACT2	UK, Denmark, Germany, Netherlands	9	2013 to 2014	18 or older years of age; eCH or cCH diagnosis	2 weeks	n=50; nNVS	n=52; Sham

Gaul et al (2016) reported on the results of a randomized open-label study of t-VNS for the prevention of chronic cluster headache.[54] 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. Gaul et al (2017) reported post-hoc, additional analyses of the PREVA study with varying definitions of response, e.g., attack frequency reductions of ≥25%, ≥75%, or ≥100 from baseline. Response consistently favored nVNS regardless of definition.[55]

Silberstein et al (2016) reported on the results of a randomized, double-blind, sham-controlled study (ACT1) for treatment of acute cluster headache attacks.[56] 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. Rescue medication was allowed after 15 minutes of nNVS or sham administration. 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). An interaction p-value for the subgroup analysis was not reported.

Goadsby et al (2018) reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of acute cluster headache attacks.[57,] 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). The interaction p-value for the subgroup analysis was statistically significant (p=0.04).

Table 10. Results of RCTs of nNVS for Prevention and Treatment of Cluster Headache

Author (year);Study	**Response (%)**	**Other efficacy outcomes**			**Quality of life or functional outcomes**	**Adverse events**
PREVENTION	**≥50% reduction in mean number of attacks (%)**	**Attack reduction from baseline per week (mean)**		**Acute medication use**	**EQ-5D-3L**	**≥1 Adverse event**
Gaul (2016, 2017); PREVA (NCT01701245)					Change from baseline	
n	93	93		Unclear	81	97
nVNS	40%	-5.9		-15	0.15	52%
SOC	8%	-2.1		-2	-0.05	49%
Treatment effect (95% CI)	NR; p<0.01	3.9 (0.5 to 7.2); p=0.02		NR	Difference=0.19 (0.05 to 0.33); p<0.01	
TREATMENT	**Response (%)**	**Pain-free at 15 min (%)**	**Sustained response (%)**			**Adverse events (%)**
Silberstein (2016); ACT1 (NCT01792817)	First attack; Pain intensity score of 0 or 1 on a 5-point scale at 15 min	≥50% of attacks	Through 60 minutes	Rescue medication use	Quality of life or functional outcome	≥1 Adverse event
Overall						
n	133	133	133	133	NR	150
nVNS	27%	12%	27%	38%		25%
Sham	15%	7%	12%	51%		40%
Treatment effect (95% CI)	NR; p=0.10	NR; p=0.33	NR; p=0.04	NR; p=0.15		
By subgroup						
Treatment by subgroup interaction p-value	NR	NR	NR	NR		
cCH subgroup						
n	48	48	48	48	NR	

Author (year);Study	Response (%)	Other efficacy outcomes			Quality of life or functional outcomes	Adverse events
nVNS	14%	5%	14%	32%		
Sham	23%	15%	15%	54%		
Treatment effect (95% CI)	NR; p=0.48	NR; p=0.36	NR; p=1.0	NR; p=0.13		
eCH subgroup						
n	85	85	85	85	NR	
nVNS	34%	16%	34%	42%		
Sham	11%	2%	11%	49%		
Treatment effect (95% CI)	NR; p=0.01	NR; p=0.04	NR; p=0.01	NR; p=0.53		
Goadsby (2018); ACT2 (NCT01958125)	Proportion of attacks; Pain intensity score of 0 or 1 on a 5-point scale at 30 min	Proportion of attacks				
Overall						
n	92	92	NR	NR	NR	102
nVNS	43%	14%				40%
Sham	28%	12%				27%
Treatment effect (95% CI)	NR; p=0.05	NR; p=0.71				
By subgroup						
Treatment by subgroup interaction p-value		p=0.04				
cCH subgroup						
n	66	66				
nVNS	37%	5%				
Sham	29%	13%				
Treatment effect (95% CI)	NR; p=0.34	NR; p=0.13				
eCH subgroup						
n	27	27				
nVNS	58%	48%				
Sham	28%	6%				
Treatment effect (95% CI)	NR; p=0.07	NR; p<0.01				

Relevance and design and conduct gaps are shown in Tables 11 and 12. The PREVA prevention study was not blinded and had no sham nVNS. The ACT1 and ACT2 treatment studies both included sham nVNS. The sham was identical in appearance, weight, visual and audible feedback, and user application and produces a low-frequency signal but did not generally cause muscle contraction. The double-blind, study treatment period was less than one month in all three RCTs which limits inference about continued response. The ACT1 and ACT2 studies did not include quality of life or functional outcomes.

Table 11. Relevance Gaps of RCTs of nNVS for Prevention and Treatment of Cluster Headache

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Gaul (2016); PREVA					1: 4 week tx period, cannot assess continued response
Silberstein (2016); ACT1				1: No quality of life or functional outcomes reported.	1: Less than 1 month tx period, cannot assess continued response
Goadsby (2018); ACT2				1: No measures of sustained pain freedom, relapse or quality of life or functional outcomes reported	1: 2 week tx period, cannot assess continued response

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Gaps of RCTs of nNVS for Prevention and Treatment of Cluster Headache

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Gaul (2016); PREVA		1: No blinding		1: Differential rate of missing data for QoL measures (higher missing in nVNS)		
Silberstein(2016); ACT1						3: Interaction p not reported for treatment by cluster headache subtype
Goadsby(2018); ACT2				1: Differential rate of return of diaries in tx groups (4% missing in nVNS vs 12% missing in sham)		

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

The RCTs also provided results from open-label periods during which patients received nVNS ranging from 2 weeks in ACT2 to 3 months inACT1. Patients continued to respond to nVNS during the open-label period. Results are shown in Table 13.

Table 13. Extended, open-label follow-up of nVNS patients from RCTs

Author (year); Study	Response (%)	Attack frequency
PREVENTION	**≥50% reduction in mean number of attacks (%)**	**Attack reduction from randomized phase per week (mean)**
Gaul (2016); PREVA (NCT01701245)		
n	45	30
4 wk follow-up	29%	2
TREATMENT	**Response (%)**	**Pain-free at 15 min (%)**
Silberstein (2016); ACT1 (NCT01792817)	First attack; Pain intensity score of 0 or 1 on a 5-point scale at 15 min	≥50% of attacks
Overall		
n	NR	NR
3 mon follow-up		
cCH subgroup		
n	48	NR
3 mon follow-up	35% (95% CI, 22 to 51%)	
eCH subgroup		
n	85	NR
3 mon follow-up	29% (95% CI, 20 to 40)	
Goadsby (2018); ACT2 (NCT01958125)	Proportion of attacks; Pain intensity score of 0 or 1 on a 5-point scale at 30 min	Proportion of attacks
Overall		
n	NR	83
2 wk follow-up		14% (95% CI NR)
cCH subgroup		
n	NR	58
2 wk follow-up		11% (95% CI NR)
eCH subgroup		
n	NR	25
2 wk follow-up		26% (95% CI NR)

Nonrandomized and Observational Studies

To assess longer term outcomes, non-randomized or observational prospective studies that capture longer periods of follow-up than the RCTs (> 1 month) and/or larger populations (with minimum n of 20) were sought. No such studies were identified.

Subsection Summary: Transcutaneous VNS for Cluster Headaches

Transcutaneous (or noninvasive) VNS has been investigated for cluster headaches in 3 RCTs. The PREVA study of prevention of cluster headache in patients with chronic cluster headache demonstrated a statistically significant increase in the proportion of patients with a 50% or greater reduction in the mean number of headache attacks and statistically significant reduction in the frequency of attacks for nVNS compared to SOC with a treatment period of 4 weeks. There was also an improvement in quality of life as measured by the EQ-5D. However, the study was not blinded.

The ACT1 and ACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. The RCTs reported slightly different outcome measures so that consistencies in magnitude of treatment effects cannot be

assessed. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1 at 15 minutes into the first attack (27% vs 15%, p=0.10) and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks (12% vs 7%, p=0.33). However, in the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2 the proportion of attacks with a pain intensity score of 0 or 1 at 30 minutes was statistically significant overall (43% vs 28%, p=0.05). The proportion of attacks that were pain-free at 15 minutes was similar in the two treatment groups overall (14% vs 12%) but a significant interaction was reported (p=0.04). There was a statistically significantly higher proportion of attacks in the episodic subgroup that were pain-free at 15 minutes in the nNVS group compared to sham (48% vs 6%, p<0.01). Quality of life and functional outcomes have not been reported. Treatment periods ranged from only 2 weeks to 1 month with extended open-label follow-up of up to 3 months. Studies designed to test the effect of nVNS in the episodic subgroup with longer treatment and follow-up and including quality of life and functional outcomes are needed.

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

Migraine Headaches

One RCT has evaluated nVNS for prevention of migraine headache compared to sham and one RCT has evaluated nNVS for treatment of acute migraine headache compared to sham nNVS. Characteristics of the trials are shown in Table 14. Results are shown in Table 15. Relevance and design and conduct gaps are in Tables 16 and 17.

Table 14. Characteristics of RCTs of nVNS for migraine prevention and treatment

					Interventions	
Author (year); Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
PREVENTION						
Silberstein (2016); EVENT	US	6	2012 to 2014	18 to 65 years of age, chronic migraine diagnosis with or without aura; <15 headache days/month over last 3 months	n=30; nVNS	n=29; sham nVNS
TREATMENT						
Tassorelli (2018), Grazzi (2018), Martelletti (2018); PRESTO	Italy	10	2016 to 2017	18 to 75 years of age, migraine diagnosis with or without aura; 3 to 8 attacks/month; <15 headache days/month over last 6 months	n=122; nVNS	n=126; Sham nVNS

The EVENT trial was a feasibility study of prevention with a sample size of 59. It was not powered to detect differences in efficacy outcomes. For the outcome of response, defined as 50% or more reduction in the number of headache days, 10% of the patients in the nVNS group versus 0% in the sham group were responders; statistically testing was not performed.

PRESTO was a multicenter, double-blind, randomized, sham-controlled trial of acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. The primary efficacy outcome was the proportion of participants who were pain-free without using rescue medication at 120 minutes. There was not a statistically significant difference in the primary outcome (30% vs 20%; p = 0.07) although it favored the nVNS group. The nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at

120 minutes (41% vs 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs 18%; p=0.02). PRESTO results did not include quality of life or functional outcomes and the double-blind treatment and follow-up period was 4 weeks. In the additional 4 weeks of acute nVNS in the open-label period, rates of pain-free response after the first treated attack (28%,) and pain relief (43.4%) were similar to the rates in the double-blind period.

Table 15. Results of RCTs of nVNS for migraine prevention and treatment

Author (year); Study	**Response (%)**	**Frequency of headache**			**Other medication use**	**Quality of life or functional outcomes**	**Adverse events (%)**
PREVENTION							
Silberstein (2016)[58]; EVENT (NCT01667250)	≥50% reduction in number of headache days	Change in baseline in number of headache days / 28 days			Acute medication		≥1 Adverse event
N	59	59			59	NR	59
nVNS	10%	-1.4			NR		57%
Sham	0%	-0.2			NR		55%
Treatment effect (95% CI)	NR	NR; p=0.56			NR; "Comparable"		NR
TREATMENT	**Pain-relief (%)**	**Pain-free (%)**	**Response over multiple attacks (%)**	**Sustained response / Relapse or recurrence over 48 hours**	**Rescue medication use**	**Quality of life or functional outcomes**	**Adverse events (%)**
Tassorelli (2018)[59], Grazzi (2018)[60], Martelletti(2018)[61]; PRESTO (NCT02686034)	Decrease in pain intensity from moderate (2) or severe (3) to mild (1) or no (0) pain on a 4-point scale at 120 minutes, first attack	Pain-free without using rescue medication at 120 minutes, first attack	Pain-free at 120 minutes for ≥50% of their attacks	Sustained pain-free response at 48 hours, first attack	Did not required rescue medication (%)		≥1 Adverse event
n	243	243	243	62	243	NR	248
nVNS	41%	22%	32%	58%	59%		18%
Sham	28%	13%	18%	69%	42%		18%
Treatment effect (95% CI)	Difference=13% (NR); p=0.03	Difference=11% (NR); p=0.07	Difference=14% (NR); p=0.02	NR; p=0.38	NR; p=0.01		

Table 16. Relevance Gaps of RCTs of nNVS for Prevention and Treatment of Migraine Headache

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Silberstein(2016); EVENT		5: ~20% of participants discontinued tx during first 2 mon	2: Sham did not deliver electrical stimulations, may have compromised blinding 4: ~20% of participants discontinued tx during first 2 mon	1: No quality of life or functional outcomes reported.	1: 2 month tx period, cannot assess continued response
Tassorelli(2018); PRESTO				1: No quality of life or functional outcomes reported	1: 4 week tx period, cannot assess continued response

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest; 5: Not delivered effectively
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 17. Study Design and Conduct Gaps of RCTs of nNVS for Prevention and Treatment of Migraine Headache

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Silberstein(2016); EVENT					1,2,3: No formal sample size calculations or efficacy hypotheses; primarily a feasibility RCT. Probably low power to detect difference in efficacy outcomes	
Tassorelli(2018); PRESTO						

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized and Observational Studies

To assess longer term outcomes, non-randomized or observational prospective studies that capture longer periods of follow-up than the RCTs (> 2 months) and/or larger populations (with minimum n of 20) were sought.

Trimboli et al (2018) reported on the preventive and acute treatment of nVNS in 41 consecutive patients with refractory primary chronic headaches (n=23 with chronic migraine) in an open-

label, prospective, noncomparative clinical audit. Response was defined as at least 30% reduction in headache days/episodes after three months of treatment. Two of 23 (9%) chronic migraine patients met the definition for responder.[62,]

Grazzi et al (2016) reported on the use of preventive nVNS in an open-label, prospective, noncomparative study of 56 women with menstrual migraine. The treatment period was 12 weeks. At the end of treatment, the mean number of headache days per month was reduced from baseline (7.2 to 4.7; $p < 0.01$). Twenty patients (39%; 95% CI, 26% to 54%) had a ≥ 50 % reduction in headache days.[63,]

Kinfe et al (2015) enrolled 20 patients with treatment-refractory migraine in this 3-month, open-label, prospective, noncomparative observational study of preventive nVNS. The number of headache days per month decreased from 14.7 to 8.9 ($p < 0.01$) between baseline and end of treatment (3 months). The migraine disability assessment (MIDAS) score improved from 26 to 15 ($p < 0.01$) [64,]

Subsection Summary: Transcutaneous VNS for Migraine Headaches
The EVENT trial was a feasibility study of prevention of migraine that was not powered to detect differences in efficacy outcomes. It does not demonstrate the efficacy of nVNS for prevention of migraine. Three noncomparative prospective studies with approximately 3 months of follow-up each have been reported. One prospective, open-label series of 23 patients with chronic migraine reported only a 9% response rate at 3 months.

One RCT has evaluated nNVS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs 20%; $p = 0.07$). However, the nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs 28%; $p=0.03$) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs 18%; $p=0.02$). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind treatment period was 4 weeks with an additional 4 weeks of open-label treatment. GIven the marginally significant primary outcome, lack of quality of life or functional outcomes and limited follow-up, further RCTs are needed

Other 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.[65,] 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.[66,] 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.[67,]

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.[68,] 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. One RCT of transcutaneous VNS for treatment of major depressive disorder has been registered in clinicaltrials.gov with a completion date of July 2016 (NCT02562703) but appears to be unpublished.

Hasan et al (2015) reported on a randomized trial of t-VNS for the treatment of schizophrenia.[69,] 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.[70,] Reviewers also included a fifth study in a data table, although not in their text or a reference list (Hein et al [2013][68,] ; previously described). Overall, the studies assessed were limited by small size and poor generalizability.

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.[71,] 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. One RCT of transcutaneous VNS for treatment of major depressive disorder is registered (NCT02562703) but appears to be unpublished. A sham-controlled pilot randomized trial for impaired glucose tolerance showed some effect on glucose

Summary of Evidence

Implantable 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 chronic cluster headache who receive noninvasive transcutaneous VNS (nVNS) to prevent cluster headache, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The PREVA study of prevention of cluster headache in patients with chronic cluster headache demonstrated a statistically significant increase in the proportion of patients who were responders (defined as 50% or greater reduction in the mean number of headache attacks; 40% versus 8% for nVNS versus standard care) and statistically significant reduction in the frequency of attacks for nVNS compared to standard care (-5.9 versus -2.1) with a treatment period of 4 weeks. There was also an improvement in quality of life as measured by the EQ-5D. However, the study was not blinded. Approximately 30% of nVNS patients had continued response during an open label follow-up of 4 weeks after the double-blind period. Longer term follow-up has not been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cluster headache who receive noninvasive transcutaneous VNS (nVNS) to treat acute cluster headache, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The ACT1 and ACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1 at 15 minutes into the first attack and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks. In the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2, the proportion of attacks with pain intensity score of 0 or 1 at 30 minutes was higher for nVNS in the overall population (43% versus 28%, p=0.05) while the proportion of attacks that were pain-free at 15 minutes was similar in the two treatment groups in the overall population (14% vs 12%). However, a statistically significantly higher proportion of attacks in the episodic subgroup (n=27) were pain-free at 15 minutes in the nNVS group compared to sham (48% vs 6%, p<0.01). These studies suggest that people with episodic and chronic cluster headaches may respond differently to acute treatment with nVNS. Studies designed to focus on episodic cluster headache are needed. Quality of life and functional outcomes have not been reported. Treatment periods ranged from only 2 weeks to 1 month with extended open-label follow-up of up to 3 months. There are few adverse events of nVNS and they are mild and transient. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with migraine headache who receive noninvasive transcutaneous VNS to treat acute migraine headache, the evidence includes 1 RCT. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. One RCT has evaluated nNVS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs 20%; p = 0.07). However, the nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs 18%; p=0.02). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind

treatment period was 4 weeks with an additional 4 weeks of open-label treatment. 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."[72,] 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)."[73,] 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).[74,]

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence issued guidance on use of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine in 2016 (IPG552).[75,] The guidance states: "Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality." The guidance also comments that further research is needed to clarify whether the procedure is used for treatment or prevention, for cluster headache or migraine, appropriate patient selection, and treatment regimen and suggests that outcome measures should include changes in the number and severity of cluster headache or migraine episodes, medication use, quality of life in the short and long term, side effects, acceptability, and device durability.

NICE also published a Medtech innovation briefing in 2018 on nVNS for cluster headache (MIB162).[76,] The briefing states that the 'intended place in therapy would be as well as standard care, most likely where standard treatments for cluster headache are ineffective, not tolerated or contraindicated' and that key uncertainties around the evidence are that 'people with episodic and chronic cluster headaches respond differently to treatment with gammaCore. The optimal use of gammaCore in the different populations in unclear.

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			
NCT03062514a	Vagus Nerve Stimulation for Pediatric Intractable Epilepsy (VNS-PIE)	84	Dec 2019
NCT02378844	A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study ofgammaCore®, a Non-invasive Vagal Nerve Stimulator (nVNS), for Prevention of Episodic Migraine	479	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
NCT01281293a	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
NCT03163030a	Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure With Preserved Ejection Fraction (ANTHEM-HFpEF) Study	50	Dec 2018
NCT03327649	Neuromodulation of Inflammation to Treat Heart Failure With Preserved Ejection Fraction	72	Dec 2019
NCT03320304a	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 (CoRaVNStiR)	40	Jul 2017 (unknown)
NCT02378792a	The Clinical Research on TsingHua Vagus Nerve Stimulator for Treatment of Refractory Epilepsy Enrollment	300	Dec 2017 (unknown)
NCT02983448	Noninvasive Neuromodulation to Reserve Diastolic Dysfunction	26	Dec 2017 (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, doe 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, doe 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	Revised title from Vagal Nerve Stimulator to Vagus Nerve Stimulation
	Added Rationale section
	In Coding section: ▪ Added L8689
	Added Revisions section
10-26-2010	Description section updated
	In Policy section: ▪ Policy language liberalized from: "Vagal nerve stimulation is medically necessary for: 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. ▪ Policy language liberalized from: "Vagal nerve stimulation is experimental / investigational because effectiveness has not been established for all other indications including: 1. Autism, 2. Obesity, 3. Refractory depression, 4. Obsessive-compulsive disorder, 5. Cognitive impairment associated with Alzheimer's disease, and 6. Depression" 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.
	Added Policy Guidelines section and the following wording: ▪ "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."
	Updated Rationale section
	In Coding section:

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	▪ Updated wording for CPT/HCPCS codes: 61886, L8681, L8689
	Updated References section
03-03-2011	In Coding section: ▪ Added CPT codes: 64568, 64569, 64570
	Rationale section updated.
	Reference section updated.
01-01-2012	In Coding section: ▪ Revised CPT nomenclature for the following code: 64553 ▪ Removed CPT code: 64573 ▪ Removed the following CPT guidelines: "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. 95975: complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, each additional 30 minutes." ▪ Added the following CPT guidelines: "95974: use modifier 52, if less than 31 minutes in duration."
08-24-2012	Description section updated.
	In the Policy section: ▪ 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."
	Rationale section updated.
	Reference section updated.
06-26-2013	Rational section updated.
	In Coding section: ▪ Added ICD-10 Diagnoses *(Effective October 1, 2014)*
11-24-2015	Description section updated
	In Policy section: ▪ 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."
	Rationale section updated
	In Coding section: ▪ Updated Coding notations.
	References updated
04-25-2016	Description section updated
	Rationale section updated
	References updated
12-21-2017	Policy published 11-21-2017. Policy effective 12-21-2017.
	Description section updated
	In Policy section: ▪ 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

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	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."
	Rationale section updated
	In Coding section: ▪ 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
	References updated
05-09-2018	Description section updated
	Rationale section updated
	References updated
01-01-2019	In Coding section: Added CPT Codes: 95976, 95977, 95983, 95984 Removed CPT Codes: 95974, 95975
05-08-2019	Description section updated
	Rationale section updated
	References updated

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