

Vagus Nerve Stimulation

Policy # 00134

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

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

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

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of vagus nerve stimulation (VNS) as a treatment in individuals with seizures other than medically refractory seizures to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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

****Note:** *This includes implantable and integrated vagus nerve neurostimulator systems (e.g., SetPoint RA system billed with CPT codes 0908T–0912T).*

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

Policy Guidelines

Vagus nerve stimulation has been evaluated for the treatment of obesity.

Background/Overview

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Table 1 includes updates on the U.S. Food and Drug Administration (FDA) approval and clearance for VNS devices pertinent to this evidence review.

Table 1. FDA Approved or Cleared Vagus Nerve Stimulators

Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
NeuroCybernetic Prosthesis (NCP®)‡	LivaNova (Cyberonics)	1997	P970003	LYJ, MUZ	Indicated or adjunctive treatment

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Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
/VNS Therapy ^{®†}					t 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

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Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
					not had an adequate response to ≥ 4 adequate antidepressant treatments
		2017	P970003/S207		Expanded indication 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

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Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
					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/ 2021	K172270/K180538/K182369/K191830/K203456/K211856	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

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Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
					e in adult patients. The acute treatment of pain associated with migraine headache in adult patients. The preventive treatment of migraine headache in adult patients.
Microtransponder [®] Vivistim [®] Paired VNS [™] system	Microtransponder Inc.	2021	210007	QPY	The device is intended to stimulate the vagus nerve during rehabilitation therapy to reduce

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Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
					upper extremity motor deficits and improve motor function in patients with chronic ischemic stroke and moderate to severe arm impairment.
SetPoint System	SetPoint Medical	2025	P240039	SFJ	Indicated for use in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate

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Device Name	Manufacturer	Approved/Cleared	PMA/510(k)	Product Code(s)	Indications
					response, loss of response, or intolerance to one or more biologic or targeted synthetic DMARDs

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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.

Summary of Evidence

Vagus Nerve Stimulation

For individuals who have seizures refractory to medical treatment who receive vagus nerve stimulation (VNS), the evidence includes randomized controlled trials (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

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broader range of seizure types in both adults and children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have treatment-resistant depression who receive VNS, the evidence includes 3 RCTs evaluating the efficacy of implanted VNS for treatment-resistant depression compared to sham, 1 RCT comparing therapeutic to low-dose implanted VNS, nonrandomized comparative studies, and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Two sham-controlled RCTs only reported short-term results and found no significant improvement in the primary outcome. One sham-controlled trial with follow-up through 12 months found no difference in Montgomery-Åsberg Depression Rating Scale (MADRS) time in response between active and sham groups; however, several clinician and self-reported measures of symptom improvement showed a benefit for 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 are limited by small sample sizes, potential selection and confounding biases, and lack of a control group in the case series. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic heart failure who receive VNS, the evidence includes a systematic review including 4 RCTs and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Meta-analyses of the RCTs evaluating chronic heart failure found significant improvements in New York Heart Association functional class, quality of life, 6-minute walk-test, and N-terminal-pro brain natriuretic peptide levels in patients treated with VNS compared to control. An analysis of the ANTHEM-HF uncontrolled trial evaluated longer-term outcomes of VNS use in chronic heart failure. They found that left ventricular (LV) ejection fraction improved by 18.7%, 19.3%, and 34.4% at 12, 24, and 36 months, respectively, with high-intensity VNS. Individuals with low-intensity VNS only had significant improvement in LV ejection fraction at 24 months (12.3%). The ANTHEM-HFpEF trial found improvements in New York Heart Association functional class, quality of life, and 6-minute walk test distances in patients with preserved ejection fraction and implanted VNS. Although this data is promising, a lack of a no-VNS comparator group precludes drawing conclusions based on findings from the uncontrolled studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have upper-limb impairment due to stroke who receive VNS, the evidence includes 3 pilot RCTs and a systematic review of these RCTs. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Two RCTs compared VNS plus rehabilitation to rehabilitation alone; 1 failed to show significant improvements for the VNS group on response and function outcomes, but the other, which had a larger patient population, found a significant difference in response and function outcomes. The other RCT compared VNS to sham and found that although VNS significantly improved response rate, there were 3 serious adverse events related to surgery. A systematic review pooling these data found that implanted VNS improved upper limb motor function based on Fugl-Meyer Assessment-Upper Extremity score when compared to control. Longer-term follow-up studies are needed to evaluate long-term efficacy and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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For adults with moderate-to-severe rheumatoid arthritis who receive VNS, the evidence includes 1 pilot randomized, sham-controlled trial and 1 multicenter sham-controlled RCT. The pilot RCT in multidrug-refractory RA demonstrated procedural feasibility and safety. The trial reported that American College of Rheumatology Score 20 [ACR20] and Disease Activity Score-28 [DAS28] outcomes were numerically superior for the VNS group; however, these differences were not statistically compared, as the study wasn't powered for effectiveness. The pivotal RESET-RA trial was a multicenter, double-blind, sham-controlled RCT with a 12-week blinded period; published peer-reviewed results show a high rate of implant success and low rates of adverse events, but do not report additional outcomes. The manufacturer's IFU reports statistical superiority of implantable VNS over sham for the prespecified primary responder endpoint, ACR20, but no significant differences on secondary clinical and functional outcomes (DAS28, The Clinical Disease Activity Index [CDAI], and Health Assessment Questionnaire Disability Index [HAQ-DI]). Safety across studies was acceptable, with mostly mild stimulation-related events and infrequent surgery-related complications. Evidence for implantable VNS remains limited to a small feasibility RCT that was not powered for efficacy, as well as a single pivotal, sham-controlled trial with outcome assessment only available in manufacturer documents, which has not yet been peer-reviewed. Overall, the certainty of evidence for RA remains limited, and an additional large, peer-reviewed RCT with longer blinded follow-up is warranted. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

Transcutaneous Vagus Nerve Stimulation

For individuals with cluster headaches who receive transcutaneous VNS (tVNS; also referred to as noninvasive VNS [nVNS]) to prevent cluster headaches, the evidence includes 1 RCT and 1 systematic review. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. One RCT for prevention of cluster headache showed a reduction in headache frequency but did not include a sham treatment group. The systematic review evaluating the same RCT found that nVNS reduced the frequency of weekly attacks and improved response rates in preventive cluster headache, however the certainty of evidence rated as low. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cluster headache who receive nVNS to treat acute cluster headache, the evidence includes RCTs and 1 systematic review. 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

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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% vs. 28%, $p=.05$) while the proportion of attacks that were pain-free at 15 minutes was similar in the 2 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 nVNS group compared to sham (48% vs. 6%, $p<.01$). 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 systematic review evaluating the same RCTs found that nVNS did not improve pain freedom, pain relief, or attack duration compared to controls, with certainty of evidence rated low to very low. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with migraine headache who receive nVNS to treat acute migraine headache, the evidence includes 1 RCT and 1 systematic review. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. One RCT has evaluated nVNS 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%; $p=.07$). 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%; $p=.03$) and a higher proportion of patients who were pain-free at 120 minutes for 50% or more of their attacks (32% vs. 18%; $p=.02$). 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. A systematic review evaluating the same RCT found that nVNS reduced short-term pain but provided no sustained benefit for pain freedom relative to control participants, with the certainty of evidence rated as moderate to low. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic migraine headache who receive nVNS to prevent migraine headache, the evidence includes 3 RCTs and 1 systematic review. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The EVENT RCT 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. The PREMIUM RCT was a phase 3, multicenter, sham-controlled RCT including 341 randomized participants with a 12-week double-blind treatment period. The results of PREMIUM demonstrated that nVNS was not statistically significantly superior to sham with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last 4 weeks, reduction in number of migraine days from baseline to the last 4 weeks, or acute medication days. The PREMIUM II trial was a multicenter, sham-controlled RCT including 231 randomized participants with a 12-week double-blind treatment period. The trial was terminated early due to the COVID-19 pandemic and results were based on a modified intention-to-treat population that included 113 total participants. Results demonstrated that treatment with

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nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12, nor other outcomes such as mean change in the number of headache days or acute medication days. However, the percentage of patients with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group than in the sham group. The systematic review found that nVNS resulted in only small reductions in monthly migraine or headache days compared with sham, and the results did not consistently achieve statistical significance. The certainty of evidence for preventive migraine was judged low to very low. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic, psychiatric, or metabolic disorders (eg, epilepsy, depression, schizophrenia, noncluster headache, impaired glucose tolerance, fibromyalgia, stroke) who receive tVNS, the evidence includes RCTs, systematic reviews of these 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 tVNS in improving patient outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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." The guidelines were updated in 2013 and reaffirmed in 2022, 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)."

American Psychiatric Association

Updated in 2010, the American Psychiatric Association guidelines for the treatment of major depressive disorder in adults 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)."

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National Institute for Health and Care Excellence

In 2016, the NICE issued guidance on use of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). 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.

In 2018, the NICE also published a Medtech innovation briefing on noninvasive VNS for cluster headache (MIB162). 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 is unclear. The NICE published a Medical technologies guidance [MTG46] on gammaCore for cluster headache in December 2019. The recommendations state that evidence supports using gammaCore to treat cluster headache and that gammaCore is not effective in everyone with cluster headache.

In 2020, the NICE published an Interventional Procedure Overview on implanted vagus nerve stimulation for treatment-resistant depression (IPG679). The guidance states: "Evidence on the safety of implanted vagus nerve stimulation for treatment-resistant depression raises no major safety concerns, but there are frequent, well-recognized side effects. Evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research." The guidance further states that "NICE encourages further research into implanted vagus nerve stimulation for treatment-resistant depression, in the form of randomized controlled trials with a placebo or sham stimulation arm. Studies should report details of patient selection. Outcomes should include validated depression rating scales, patient-reported quality of life, time to onset of effect and duration of effect, and any changes in concurrent treatment."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) has a national coverage determination for VNS. Medicare coverage policy notes that "Clinical evidence has shown that vagus nerve stimulation is safe and effective treatment for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. Vagus nerve stimulation is not covered for patients with other types of seizure disorders that are medically refractory and for whom surgery is not recommended or for whom surgery has failed." [Centers for Medicare & Medicaid Services (CMS). Na....

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In response to a request from LivaNova, on May 30, 2018, CMS initiated its second reconsideration of its national coverage decision on VNS for Treatment Resistant Depression (TRD). Based on an internal literature review (search dates unspecified), CMS concluded that although the published evidence suggests that VNS is a promising treatment for patients with TRD, the reviewed studies have important flaws that leave uncertainty about its true benefits and harms. Thus, effective February 15, 2019, the CMS expanded Medicare coverage to "cover U.S. Food and Drug Administration approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim findings." CMS approval of a Coverage with Evidence Development study requires answering 9 research questions specifying measurement of response, remission, harms and other health outcome variables, use of specific eligibility criteria for TRD diagnosis as described in an Agency for Healthcare Research and Quality Technology Assessment conducted by Gaynes et al (2018), as well as 13 additional operational criteria. CMS has approved 1 ongoing study for Coverage with Evidence Development - A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy^{®‡} System as Adjunctive Therapy Versus a No Stimulation Control in Subjects With Treatment-Resistant Depression (RECOVER) (NCT03887715). Conway et al (2020) have published a detailed description of the RECOVER study rationale and design.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03320304 ^a	A Global Prospective, Multi-center, Observational Post-market Study to Assess short, Mid and Long-term Effectiveness and Efficiency of VNS Therapy ^{®‡} as Adjunctive Therapy in real-world patients with difficult to Treat depression	500	Dec 2028
NCT03887715 ^a	A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy ^{®‡} System as Adjunctive Therapy Versus a No Stimulation Control in Subjects with Treatment-Resistant Depression (RECOVER)	6800	Dec 2030

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NCT04935567	Prediction of Vagal Nerve Stimulation Efficacy in Drug-resistant Epilepsy: Prospective Study for Pre-implantation Prediction	120	Dec 2026
NCT04777500	Applying Transcutaneous Auricular Vagus Nerve Stimulation to Treat Fibromyalgia	60	Mar 2027
NCT04534556	Wireless Nerve Stimulation Device to Enhance Recovery After Stroke	30	Jan 2025 (unknown)
NCT04448327	Sex-Dependent Impact of Transcutaneous Vagal Nerve Stimulation on the Stress Response Circuitry and Autonomic Dysregulation in Major Depression	80	Dec 2025
NCT04539964 ^a	Vagus Nerve Stimulation Using the SetPoint System for Moderate to Severe Rheumatoid Arthritis: The RESET-RA Study	243	Oct 2027
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)
NCT01281293 ^a	A Post Market, Long Term, Observational, Multi-site Outcome Study to Follow the Clinical Course and Seizure Reduction of Patients with Refractory Seizures Who Are Being Treated with Adjunctive VNS Therapy	124	Aug 2018
NCT03380156	Effect of Transcutaneous Vagal Stimulation (TVS) on Endothelial Function and Arterial Stiffness in Patients with Heart Failure with Reduced Ejection Fraction	50	May 2020
NCT04926415	Effects of Transcutaneous Auricular Vagus Nerve Stimulation on Obesity and Insulin Resistance	30	Apr 2022

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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1. Panebianco M, Rigby A, Weston J, et al. Vagus nerve stimulation for partial seizures. *Cochrane Database Syst Rev.* Apr 03 2015; 2015(4): CD002896. PMID 25835947
2. Panebianco M, Rigby A, Marson AG. Vagus nerve stimulation for focal seizures. *Cochrane Database Syst Rev.* Jul 14 2022; 7(7): CD002896. PMID 35833911
3. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg.* Dec 2011; 115(6): 1248-55. PMID 21838505
4. Ben-Menachem E, Hellström K, Waldton C, et al. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. *Neurology.* Apr 12 1999; 52(6): 1265-7. PMID 10214754
5. Parker AP, Polkey CE, Binnie CD, et al. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics.* Apr 1999; 103(4 Pt 1): 778-82. PMID 10103302
6. Labar D, Murphy J, Tecoma E. Vagus nerve stimulation for medication-resistant generalized epilepsy. E04 VNS Study Group. *Neurology.* Apr 22 1999; 52(7): 1510-2. PMID 10227649
7. DeGiorgio C, Heck C, Bunch S, et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. *Neurology.* Jul 26 2005; 65(2): 317-9. PMID 16043810
8. Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy Behav.* Jun 2003; 4(3): 302-9. PMID 12791333
9. Vonck K, Boon P, D'Havé M, et al. Long-term results of vagus nerve stimulation in refractory epilepsy. *Seizure.* Sep 1999; 8(6): 328-34. PMID 10512772
10. Vonck K, Thadani V, Gilbert K, et al. Vagus nerve stimulation for refractory epilepsy: a transatlantic experience. *J Clin Neurophysiol.* 2004; 21(4): 283-9. PMID 15509917
11. Majoie HJ, Berfelo MW, Aldenkamp AP, et al. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: clinical results, neuropsychological effects, and cost-effectiveness. *J Clin Neurophysiol.* Sep 2001; 18(5): 419-28. PMID 11709647
12. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry.* Feb 15 2002; 51(4): 280-7. PMID 11958778
13. Huf RL, Mamelak A, Kneedy-Cayem K. Vagus nerve stimulation therapy: 2-year prospective open-label study of 40 subjects with refractory epilepsy and low IQ who are living in long-term care facilities. *Epilepsy Behav.* May 2005; 6(3): 417-23. PMID 15820352
14. Kang HC, Hwang YS, Kim DS, et al. Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study. *Acta Neurochir Suppl.* 2006; 99: 93-6. PMID 17370772
15. Ardesch JJ, Buschman HP, Wagener-Schimmel LJ, et al. Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study. *Seizure.* Oct 2007; 16(7): 579-85. PMID 17543546
16. Michael JE, Wegener K, Barnes DW. Vagus nerve stimulation for intractable seizures: one year follow-up. *J Neurosci Nurs.* Dec 1993; 25(6): 362-6. PMID 8106830
17. Ben-Menachem E, Mañon-Espallat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. *Epilepsia.* 1994; 35(3): 616-26. PMID 8026408

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18. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. *Neurology*. Jul 1998; 51(1): 48-55. PMID 9674777
19. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol*. Sep 2012; 54(9): 855-61. PMID 22540141
20. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. *Epilepsia*. Jun 2014; 55(6): 893-900. PMID 24754318
21. Englot DJ, Rolston JD, Wright CW, et al. Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. *Neurosurgery*. Sep 2016; 79(3): 345-53. PMID 26645965
22. García-Navarrete E, Torres CV, Gallego I, et al. Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication. *Seizure*. Jan 2013; 22(1): 9-13. PMID 23041031
23. Hornig GW, Murphy JV, Schallert G, et al. Left vagus nerve stimulation in children with refractory epilepsy: an update. *South Med J*. May 1997; 90(5): 484-8. PMID 9160063
24. Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. *J Pediatr*. May 1999; 134(5): 563-6. PMID 10228290
25. Patwardhan RV, Stong B, Bebin EM, et al. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. *Neurosurgery*. Dec 2000; 47(6): 1353-7; discussion 1357-8. PMID 11126906
26. Frost M, Gates J, Helmers SL, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *Epilepsia*. Sep 2001; 42(9): 1148-52. PMID 11580762
27. You SJ, Kang HC, Kim HD, et al. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience. *J Korean Med Sci*. Jun 2007; 22(3): 442-5. PMID 17596651
28. Cukiert A, Cukiert CM, Burattini JA, et al. A prospective long-term study on the outcome after vagus nerve stimulation at maximally tolerated current intensity in a cohort of children with refractory secondary generalized epilepsy. *Neuromodulation*. 2013; 16(6): 551-6; discussion 556. PMID 23738578
29. Healy S, Lang J, Te Water Naude J, et al. Vagal nerve stimulation in children under 12 years old with medically intractable epilepsy. *Childs Nerv Syst*. Nov 2013; 29(11): 2095-9. PMID 23681311
30. Terra VC, Furlanetti LL, Nunes AA, et al. Vagus nerve stimulation in pediatric patients: Is it really worthwhile?. *Epilepsy Behav*. Feb 2014; 31: 329-33. PMID 24210463
31. Yu C, Ramgopal S, Libenson M, et al. Outcomes of vagal nerve stimulation in a pediatric population: a single center experience. *Seizure*. Feb 2014; 23(2): 105-11. PMID 24309238
32. Maleknia P, McWilliams TD, Barkley A, et al. Postoperative seizure freedom after vagus nerve stimulator placement in children 6 years of age and younger. *J Neurosurg Pediatr*. Apr 01 2023; 31(4): 329-332. PMID 36670534

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33. Daban C, Martinez-Aran A, Cruz N, et al. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. *J Affect Disord.* Sep 2008; 110(1-2): 1-15. PMID 18374988
34. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry.* Sep 01 2005; 58(5): 347-54. PMID 16139580
35. Food and Drug Administration. Summary of Safety and Effectiveness Data: VNS Therapy TM System. 2005; https://www.accessdata.fda.gov/cdrh_docs/pdf/p970003s050b.pdf.
36. Martin JL, Martín-Sánchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: variable results based on study designs. *Eur Psychiatry.* Apr 2012; 27(3): 147-55. PMID 22137776
37. Berry SM, Broglio K, Bunker M, et al. A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. *Med Devices (Auckl).* 2013; 6: 17-35. PMID 23482508
38. Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *J Clin Psychopharmacol.* Jun 2010; 30(3): 273-81. PMID 20473062
39. Aaronson ST, Carpenter LL, Conway CR, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. *Brain Stimul.* Jul 2013; 6(4): 631-40. PMID 23122916
40. Bottomley JM, LeReun C, Diamantopoulos A, et al. Vagus nerve stimulation (VNS) therapy in patients with treatment resistant depression: A systematic review and meta-analysis. *Compr Psychiatry.* Dec 12 2019; 98: 152156. PMID 31978785
41. Conway CR, Aaronson ST, Sackeim HA, et al. Vagus nerve stimulation in treatment-resistant depression: A one-year, randomized, sham-controlled trial. *Brain Stimul.* 2025; 18(3): 676-689. PMID 39706521
42. Rush AJ, Conway CR, Aaronson ST, et al. Effects of vagus nerve stimulation on daily function and quality of life in markedly treatment-resistant major depression: Findings from a one-year, randomized, sham-controlled trial. *Brain Stimul.* 2025; 18(3): 690-700. PMID 39701918
43. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry.* Sep 01 2005; 58(5): 364-73. PMID 16139582
44. De Ferrari GM, Crijns HJ, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J.* Apr 2011; 32(7): 847-55. PMID 21030409
45. Aaronson ST, Sears P, Ruvuna F, et al. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. *Am J Psychiatry.* Jul 01 2017; 174(7): 640-648. PMID 28359201
46. McAllister-Williams RH, Sousa S, Kumar A, et al. The effects of vagus nerve stimulation on the course and outcomes of patients with bipolar disorder in a treatment-resistant depressive episode: a 5-year prospective registry. *Int J Bipolar Disord.* May 02 2020; 8(1): 13. PMID 32358769
47. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biol Psychiatry.* Feb 15 2000; 47(4): 276-86. PMID 10686262

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Current Effective Date: 06/01/2026

48. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. Nov 2001; 25(5): 713-28. PMID 11682255
49. Marangell LB, Suppes T, Zboyan HA, et al. A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry*. Feb 2008; 69(2): 183-9. PMID 18211128
50. Tisi G, Franzini A, Messina G, et al. Vagus nerve stimulation therapy in treatment-resistant depression: a series report. *Psychiatry Clin Neurosci*. Aug 2014; 68(8): 606-11. PMID 25215365
51. Sant'Anna LB, Couceiro SLM, Ferreira EA, et al. Vagal Neuromodulation in Chronic Heart Failure With Reduced Ejection Fraction: A Systematic Review and Meta-Analysis. *Front Cardiovasc Med*. 2021; 8: 766676. PMID 34901227
52. Premchand RK, Sharma K, Mittal S, et al. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail*. Nov 2014; 20(11): 808-16. PMID 25187002
53. Nearing BD, Libbus I, Carlson GM, et al. Chronic vagus nerve stimulation is associated with multi-year improvement in intrinsic heart rate recovery and left ventricular ejection fraction in ANTHEM-HF. *Clin Auton Res*. Jun 2021; 31(3): 453-462. PMID 33590355
54. Kumar HU, Nearing BD, Mittal S, et al. Autonomic regulation therapy in chronic heart failure with preserved/mildly reduced ejection fraction: ANTHEM-HFpEF study results. *Int J Cardiol*. Jun 15 2023; 381: 37-44. PMID 36934987
55. Ramos-Castaneda JA, Barreto-Cortes CF, Losada-Florian D, et al. Efficacy and Safety of Vagus Nerve Stimulation on Upper Limb Motor Recovery After Stroke. A Systematic Review and Meta-Analysis. *Front Neurol*. 2022; 13: 889953. PMID 35847207
56. Dawson J, Pierce D, Dixit A, et al. Safety, Feasibility, and Efficacy of Vagus Nerve Stimulation Paired With Upper-Limb Rehabilitation After Ischemic Stroke. *Stroke*. Jan 2016; 47(1): 143-50. PMID 26645257
57. Dawson J, Liu CY, Francisco GE, et al. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet*. Apr 24 2021; 397(10284): 1545-1553. PMID 33894832
58. Kimberley TJ, Pierce D, Prudente CN, et al. Vagus Nerve Stimulation Paired With Upper Limb Rehabilitation After Chronic Stroke. *Stroke*. Nov 2018; 49(11): 2789-2792. PMID 30355189
59. Lange G, Janal MN, Maniker A, et al. Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. *Pain Med*. Sep 2011; 12(9): 1406-13. PMID 21812908
60. De Ridder D, Vanneste S, Engineer ND, et al. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. *Neuromodulation*. Feb 2014; 17(2): 170-9. PMID 24255953
61. Engineer CT, Hays SA, Kilgard MP. Vagus nerve stimulation as a potential adjuvant to behavioral therapy for autism and other neurodevelopmental disorders. *J Neurodev Disord*. 2017; 9: 20. PMID 28690686
62. International Headache Society. International Classification of Headache Disorders. 2018; <https://www.ichd-3.org>.

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Original Effective Date: 06/05/2002

Current Effective Date: 06/01/2026

63. Jokic M, Lee C, Holubowich C, et al. Noninvasive Vagus Nerve Stimulation for Cluster Headache and Migraine: A Health Technology Assessment. *Ont Health Technol Assess Ser.* 2025; 25(2): 1-177. PMID 40496978
64. Gaul C, Diener HC, Silver N, et al. Non-invasive vagus nerve stimulation for PREvention and Acute treatment of chronic cluster headache (PREVA): A randomised controlled study. *Cephalalgia.* May 2016; 36(6): 534-46. PMID 26391457
65. Gaul C, Magis D, Liebler E, et al. Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the randomised, controlled PREVA study. *J Headache Pain.* Dec 2017; 18(1): 22. PMID 28197844
66. Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia.* Jan 2012; 32(1): 6-38. PMID 22384463
67. Silberstein SD, Mechtler LL, Kudrow DB, et al. Non-Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study. *Headache.* Sep 2016; 56(8): 1317-32. PMID 27593728
68. Goadsby PJ, de Coo IF, Silver N, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A randomized, double-blind, sham-controlled ACT2 study. *Cephalalgia.* Apr 2018; 38(5): 959-969. PMID 29231763
69. de Coo IF, Marin JC, Silberstein SD, et al. Differential efficacy of non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: A meta-analysis. *Cephalalgia.* Jul 2019; 39(8): 967-977. PMID 31246132
70. Tassorelli C, Grazi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. *Neurology.* Jul 24 2018; 91(4): e364-e373. PMID 29907608
71. Grazi L, Tassorelli C, de Tommaso M, et al. Practical and clinical utility of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: a post hoc analysis of the randomized, sham-controlled, double-blind PRESTO trial. *J Headache Pain.* Oct 19 2018; 19(1): 98. PMID 30340460
72. Martelletti P, Barbanti P, Grazi L, et al. Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: additional findings from the randomized, sham-controlled, double-blind PRESTO trial. *J Headache Pain.* Nov 01 2018; 19(1): 101. PMID 30382909
73. Trimboli M, Al-Kaisy A, Andreou AP, et al. Non-invasive vagus nerve stimulation for the management of refractory primary chronic headaches: A real-world experience. *Cephalalgia.* Jun 2018; 38(7): 1276-1285. PMID 28899205
74. Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study. *Neurology.* Aug 02 2016; 87(5): 529-38. PMID 27412146
75. Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled PREMIUM trial. *Cephalalgia.* Oct 2019; 39(12): 1475-1487. PMID 31522546
76. Najib U, Smith T, Hindiyeh N, et al. Non-invasive vagus nerve stimulation for prevention of migraine: The multicenter, randomized, double-blind, sham-controlled PREMIUM II trial. *Cephalalgia.* Jun 2022; 42(7): 560-569. PMID 35001643

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77. Grazzi L, Egeo G, Calhoun AH, et al. Non-invasive Vagus Nerve Stimulation (nVNS) as mini-prophylaxis for menstrual/menstrually related migraine: an open-label study. *J Headache Pain*. Dec 2016; 17(1): 91. PMID 27699586
78. Kinfte TM, Pintea B, Muhammad S, et al. Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: a prospective observational cohort study. *J Headache Pain*. 2015; 16: 101. PMID 26631234
79. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. *Arthritis Rheum*. Mar 15 2007; 57(2): 193-202. PMID 17330293
80. Curtis JR, Yang S, Chen L, et al. Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients. *Arthritis Care Res (Hoboken)*. Oct 2015; 67(10): 1345-53. PMID 25988705
81. Johnson TM, Michaud K, England BR. Measures of rheumatoid arthritis disease activity. *Arthritis Care Res*. 2020;72(suppl 10):4-26. doi:10.1002/acr.24336.
82. Strand V, van Vollenhoven RF, Lee EB, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. *Rheumatology (Oxford)*. Jun 2016; 55(6): 1031-41. PMID 26929445
83. Genovese MC, Gaylis NB, Sikes D, et al. Safety and efficacy of neurostimulation with a miniaturised vagus nerve stimulation device in patients with multidrug-refractory rheumatoid arthritis: a two-stage multicentre, randomised pilot study. *Lancet Rheumatol*. Sep 2020; 2(9): e527-e538. PMID 38273617
84. Peterson D, Van Poppel M, Boling W, et al. Clinical safety and feasibility of a novel implantable neuroimmune modulation device for the treatment of rheumatoid arthritis: initial results from the randomized, double-blind, sham-controlled RESET-RA study. *Bioelectron Med*. Mar 13 2024; 10(1): 8. PMID 38475923
85. SetPoint Medical. SetPoint System: Surgeon Instructions for Use. https://setpointmedical.com/wp-content/uploads/DWG_65154_Surgeon_IFUv2.pdf.
86. Aihua L, Lu S, Liping L, et al. A controlled trial of transcutaneous vagus nerve stimulation for the treatment of pharmacoresistant epilepsy. *Epilepsy Behav*. Oct 2014; 39: 105-10. PMID 25240121
87. Bauer S, Baier H, Baumgartner C, et al. Transcutaneous Vagus Nerve Stimulation (tVNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial (cMPsE02). *Brain Stimul*. 2016; 9(3): 356-363. PMID 27033012
88. Rong P, Liu A, Zhang J, et al. Transcutaneous vagus nerve stimulation for refractory epilepsy: a randomized controlled trial. *Clin Sci (Lond)*. Apr 01 2014. PMID 24684603
89. Wu K, Wang Z, Zhang Y, et al. Transcutaneous vagus nerve stimulation for the treatment of drug-resistant epilepsy: a meta-analysis and systematic review. *ANZ J Surg*. Apr 2020; 90(4): 467-471. PMID 32052569
90. Yang H, Shi W, Fan J, et al. Transcutaneous Auricular Vagus Nerve Stimulation (ta-VNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial. *Neurotherapeutics*. Apr 2023; 20(3): 870-880. PMID 36995682

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91. Shi J, Lu D, Wei P, et al. Comparative Efficacy of Neuromodulatory Strategies for Drug-Resistant Epilepsy: A Systematic Review and Meta-Analysis. *World Neurosurg.* Jan 2025; 193: 373-396. PMID 39321920
92. Hasan A, Wolff-Menzler C, Pfeiffer S, et al. Transcutaneous noninvasive vagus nerve stimulation (tVNS) in the treatment of schizophrenia: a bicentric randomized controlled pilot study. *Eur Arch Psychiatry Clin Neurosci.* Oct 2015; 265(7): 589-600. PMID 26210303
93. Shiozawa P, Silva ME, Carvalho TC, et al. Transcutaneous vagus and trigeminal nerve stimulation for neuropsychiatric disorders: a systematic review. *Arq Neuropsiquiatr.* Jul 2014; 72(7): 542-7. PMID 25054988
94. Hein E, Nowak M, Kiess O, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. *J Neural Transm (Vienna).* May 2013; 120(5): 821-7. PMID 23117749
95. Huang F, Dong J, Kong J, et al. Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: a pilot randomized study. *BMC Complement Altern Med.* Jun 26 2014; 14: 203. PMID 24968966
96. Wu D, Ma J, Zhang L, et al. Effect and Safety of Transcutaneous Auricular Vagus Nerve Stimulation on Recovery of Upper Limb Motor Function in Subacute Ischemic Stroke Patients: A Randomized Pilot Study. *Neural Plast.* 2020; 2020: 8841752. PMID 32802039
97. Kutlu N, Özden AV, Alptekin HK, et al. The Impact of Auricular Vagus Nerve Stimulation on Pain and Life Quality in Patients with Fibromyalgia Syndrome. *Biomed Res Int.* 2020; 2020: 8656218. PMID 32190684
98. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy [RETIRED]: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* Sep 11 1999; 53(4): 666-9. PMID 10489023
99. Morris GL, Gloss D, Buchhalter J, et al. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* Oct 15 2013; 81(16): 1453-9. PMID 23986299
100. American Psychiatric Association, Work Group on Major Depressive Disorder, Gelenberg Aj, et al. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. Third Edition. 2010; 3rd ed.:https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.
101. National Institute for Health and Care Excellence. Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). 2016; <https://www.nice.org.uk/guidance/ipg552>.
102. National Institute for Health and Care Excellence. gammaCore for cluster headache (MIB162). 2018. <https://www.nice.org.uk/advice/mib162>.
103. National Institute for Health and Care Excellence. Medical technologies guidance [MTG46]: gammaCore for cluster headache. December 2019. <https://www.nice.org.uk/guidance/MTG46>.
104. National Institute for Health and Care Excellence. Implanted vagus nerve stimulation for treatment-resistant depression - Interventional Procedures Guidance (IPG679). 2020; <https://www.nice.org.uk/guidance/ipg679/chapter/1-Recommendations>.

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Current Effective Date: 06/01/2026

105. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for VAGUS Nerve Stimulation (VNS) (160.18). 2019; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=230>.
106. Centers for Medicare & Medicaid Services (CMS). Decision Memo for Vagus Nerve Stimulation for Treatment Resistant Depression (TRD) (CAG-00313R2). February 2019; <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=292&NCDId=230>.
107. Gaynes BN, Asher G, Gartlehner G, Hoffman V, Green J, Bolland E, Lux L, Weber RP, Randolph C, Bann C, Coker-Schwimmer E, Viswanathan M, Lohr KN. Definition of Treatment-Resistant Depression in the Medicare Population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Feb 9. PMID: 30260611.
108. Centers for Medicare & Medicaid Services. Coverage with Evidence Development for Vagus Nerve Stimulation for Treatment Resistant Depression. 2024. <https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/VNS>.
109. Conway CR, Olin B, Aaronson ST, et al. A prospective, multi-center randomized, controlled, blinded trial of vagus nerve stimulation for difficult to treat depression: A novel design for a novel treatment. Contemp Clin Trials. Aug 2020; 95: 106066. PMID 32569757

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03/21/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. No substance change to policy.
06/28/2004	Managed Care Advisory Council approval
06/07/2005	Medical Director review
06/21/2005	Medical Policy Committee review. Clinical criteria revised to add investigational statement for VNS treatment for essential tremor
07/15/2005	Managed Care Advisory Council Approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged
08/04/2006	Medical Director Review
08/09/2006	Medical Policy Committee approval
11/07/2007	Medical Director Review
11/15/2007	Medical Policy Committee approval. Added headaches to the investigational policy statement.
11/05/2008	Medical Director Review
11/18/2008	Medical Policy Committee approval. No change to coverage eligibility.
11/12/2009	Medical Policy Committee approval

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11/18/2009	Medical Policy Implementation Committee approval. Deleted “partial-onset” verbiage from “medically refractory seizures” in the coverage section. Added the treatment of obesity as an investigational indication.
11/04/2011	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/31/2010	Coding updated.
11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Added heart failure and fibromyalgia to the list of investigational indications.
01/23/2013	Coding updated
11/07/2013	Medical Policy Committee review
11/20/2013	Medical Policy Implementation Committee approval. No change to coverage.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Policy statement updated to include the addition of tinnitus and traumatic brain injury to the list of investigational conditions. “Based on review of available data, the Company considers non implantable vagus nerve stimulation (VNS) devices for all indications to be investigational” was added to the investigational section.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. No change to coverage. FDA updated.
01/01/2019	Coding update
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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09/30/2021	Coding update
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/07/2022	Coding update
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/12/2023	Coding update
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2025	Medical Policy Committee review
05/13/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2026	Coding Update
05/07/2026	Medical Policy Committee review
05/13/2026	Medical Policy Implementation Committee approval. Added rheumatoid arthritis to the investigational statement. "Based on review of available data, the Company considers the use of vagus nerve stimulation (VNS) as a treatment in individuals with seizures other than medically refractory seizures" was changed from investigational to not medically necessary. Added a note "This includes implantable and integrated vagus nerve neurostimulator systems (e.g., SetPoint RA system billed with CPT codes 0908T–0912T)."

Next Scheduled Review Date: 05/2027

Coding

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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Code Type	Code
CPT	61885, 61886, 61888, 64553, 64568, 64569, 64570, 95976, 95977 Add codes effective 06/01/2026: 0908T, 0909T, 0910T, 0911T, 0912T
HCPCS	C1607, C1767, C1778, C1787, C1816, C1820, C1822, C1827, C1883, E0735, L8679, L8680, L8681, L8682, L8683, L8685, L8686, L8687, L8688, L8689, L8695
ICD-10 Diagnosis	All Related Diagnoses

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

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services

Vagus Nerve Stimulation

Policy # 00134

Original Effective Date: 06/05/2002

Current Effective Date: 06/01/2026

at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

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

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.