MASSACHUSETTS

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Medical Policy
Vagus Nerve Stimulation

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Policy Number: 474

BCBSA Reference Number: 7.01.20 (For Plan internal use only)

Related Policies

- Meniscal Allografts and Other Meniscal Implants, #110
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- Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy, #716
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Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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

Vagus nerve stimulation is considered **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.

Transcutaneous (nonimplantable) vagus nerve stimulation devices are considered **INVESTIGATIONAL** for all indications.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for situations where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

CPT codes:	Code Description
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 electrodes; cranial nerve
64568	Incision for implantation 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

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

ICD-10-CM Diagnosis codes:	Code Description
G40.309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.001	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, with status epilepticus
G40.009	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, without 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
G40.109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without 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
G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without 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
G40.409	Other generalized epilepsy and epileptic syndromes, not intractable, without 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
G40.42	Cyclin-Dependent Kinase-Like 5 Deficiency Disorder
G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus
G40.509	Epileptic seizures related to external causes, not intractable, without status epilepticus
G40.801	Other epilepsy, not intractable, with status epilepticus
G40.802	Other epilepsy, not intractable, without status epilepticus
G40.803	Other epilepsy, intractable, with status epilepticus
G40.804	Other epilepsy, intractable, without status epilepticus
G40.811	Lennox-Gastaut syndrome, not intractable, with status epilepticus
G40.812	Lennox-Gastaut syndrome, not intractable, without 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
G40.822	Epileptic spasms, not intractable, without status epilepticus
G40.823	Epileptic spasms, intractable, with status epilepticus
G40.824	Epileptic spasms, intractable, without status epilepticus
G40.833	Dravet syndrome, intractable, with status epilepticus
G40.834	Dravet syndrome, intractable, without status epilepticus
G40.89	Other seizures
G40.901	Epilepsy, unspecified, not intractable, with status epilepticus
G40.909	Epilepsy, unspecified, not intractable, without status epilepticus
G40.911	Epilepsy, unspecified, intractable, with status epilepticus
G40.919	Epilepsy, unspecified, intractable, without status epilepticus
G40.A01	Absence epileptic syndrome, not intractable, with status epilepticus
G40.A09	Absence epileptic syndrome, not intractable, without 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.B09	Juvenile myoclonic epilepsy, not intractable, without status epilepticus
G40.B11	Juvenile myoclonic epilepsy, intractable, with status epilepticus
G40.B19	Juvenile myoclonic epilepsy, intractable, without status epilepticus
G40.C01	Lafora progressive myoclonus epilepsy, not intractable, with status epilepticus
G40.C09	Lafora progressive myoclonus epilepsy, not intractable, without status epilepticus
G40.C11	Lafora progressive myoclonus epilepsy, intractable, with status epilepticus
G40.C19	Lafora progressive myoclonus epilepsy, intractable, without status epilepticus
R56.9	Unspecified convulsions

The following HCPCS code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
E0735	Non-invasive vagus nerve stimulator

Description

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.

Summary

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.

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 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 2 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. The sham-controlled RCTs only reported short-term results and found no significant improvement in the primary outcome. 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.

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. 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 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. 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% 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 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. 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. 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. 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 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 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.

Policy History

Date	Action
4/2024	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2024	Clarified coding information.
10/2023	Clarified coding information.
4/2023	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
3/2022	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
4/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged. Clarified coding information.
1/2021	Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.
10/2020	Clarified coding changes.
4/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
4/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
1/2019	Clarified coding changes.
6/2018	Annual policy review. No changes to policy statements.
5/2018	New references added from annual policy review. Background and summary clarified. Prior Authorization Information reformatted.
12/2017	Annual policy review. New investigational indications described. Clarified coding information. Effective 3/1/2018.
3/2016	Annual policy review. New references added.
5/2015	Annual policy review. New references added.
8/2014	Annual policy review. New investigational indications described. Effective 8/1/2014.
6/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
12/2013	Removed the HCPCS codes (L8680-LL8689) as they do not meet the intent.
10/2013	Removed CPT codes 64569, 64570 as these CPT codes do not apply to the policy.
4/2013	Annual policy review. New references added.
2/2013	Annual policy review. Changes made to policy statements. Effective 2/4/2013.
1/2013	Updated to add new CPT codes 0312T-0317T.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
4/2011	Annual policy review. No changes to policy statements.
1/2011	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
1/2010	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
1/2009	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
1/2008	Annual policy review. No changes to policy statements.
1/2008	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
7/2007	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
2/2007	Reviewed - Medical Policy Group - Psychiatry and Ophthalmology. No changes to policy statements.
1/2007	Reviewed - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

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-Espaillat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994; 35(3): 616-26. PMID 8026408
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
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. Accessed December 23, 2023.
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. 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
42. 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

43. 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
44. 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
45. 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
46. 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
47. 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
48. 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
49. 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
50. 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
51. 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
52. 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
53. Ramos-Castaneda JA, Barreto-Cortes CF, Losada-Floriano 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
54. 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
55. 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
56. 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
57. 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
58. 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
59. 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
60. International Headache Society. International Classification of Headache Disorders. 2018; https://www.ichd-3.org. Accessed December 21, 2023.
61. 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
62. 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

63. 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
64. 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
65. 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
66. 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
67. Tassorelli C, Grazzi 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
68. Grazzi 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
69. Martelletti P, Barbanti P, Grazzi 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
70. 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
71. 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
72. 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
73. 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
74. 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
75. Kinfe 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
76. 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
77. 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
78. 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
79. 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
80. 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
81. 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

82. 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
83. 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
84. 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
85. 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
86. 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
87. Fisher RS, Handforth A. Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. Sep 11 1999; 53(4): 666-9. PMID 10489023
88. 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
89. 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. Accessed December 21, 2023.
90. 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. Accessed December 23, 2023.
91. National Institute for Health and Care Excellence. gammaCore for cluster headache (MIB162). 2018. https://www.nice.org.uk/advice/mib162. Accessed December 24, 2023.
92. National Institute for Health and Care Excellence. Medical technologies guidance [MTG46]: gammaCore for cluster headache. December 2019. https://www.nice.org.uk/guidance/MTG46. Accessed December 22, 2023.
93. 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. Accessed December 21, 2023.
94. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for VAGUS Nerve Stimulation (VNS) (160.18). 2007; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=230. Accessed December 21, 2023.
95. 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. Accessed December 21, 2023.
96. Gaynes BN, Asher G, Gartlehner G, Hoffman V, Green J, Boland 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.
97. Centers for Medicare & Medicaid Services. Coverage with Evidence Development for Vagus Nerve Stimulation for Treatment Resistant Depression. 2021. https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/VNS. Accessed December 21, 2023.
98. 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