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| **Subject:** Vagal Nerve Stimulation (VNS) | | **Original Effective Date:** 4/25/07 |
| **Policy Number:** MCR-006 | **Revision Date(s):** 6/19/08, 12/14/11, 6/12/14 *This MCR is no longer scheduled for revisions* | |
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## DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [5]

*Vagal Nerve Stimulation*

A vagal nerve stimulator is composed of an implantable generator, electrodes and an external programming device. The generator is implanted under the collar bone and operates like a. A pacemaker connected by wire to the vagus nerve where it delivers short bursts of electrical signals to the brain to control seizures. The pulse generator is programmed externally through the skin using a computer, special software and a programming wand. Parameters of stimulation that can be programmed include amplitude, pulse width, pulse train frequency, and pulse train on and off times. Patients are educated on how to control the stimulator by using a hand held magnet, the magnet can be worn on the wrist, or clipped onto clothing. The stimulator can be turned on by holding the magnet near the vagus nerve device for approximately 1-2 seconds when the onset of a seizure is sensed. The patient can turn off the stimulator if a malfunction occurs or if any discomfort is experienced by leaving the magnet over the stimulator. The device reactivates once the magnet is removed. The battery powered generator may require replacement every one and one half to five years.

The basic principles of VNS when used as a treatment for epilepsy are that vagal visceral afferents (nerves that convey impulses from sender organs and other receptors to the brain or spinal cord) have a diffuse central nervous system projection, and the activation of these pathways has a widespread effect upon neuronal excitability. The exact mechanism of VNS neuronal excitability is not fully known.

Most commonly reported complications associated with VNS are: voice alteration, hoarseness, throat pain, coughing, shortness of breath, tingling and muscle pain all noted mainly during the delivery of high stimulation. The adjustment of the amount of stimulation can decrease or eliminate the side effects experienced. Other potential complications that may occur include injury to the carotid artery or internal jugular vein and infection at the site of implantation.

*Epilepsy and Seizure:* [3]

Seizures have been defined as paroxysmal disorders of the central nervous system characterized by abnormal cerebral neuronal discharge, with or without loss of consciousness. Seizures are further classified into those with generalized onset (beginning throughout the brain), and those with partial onset (having a discrete focal onset). The following are three subtypes of partial onset seizures:

- *Simple partial seizures:* Simple partial seizures begin with an electrical discharge in one limited area of the brain. Some are related to head injury, brain infection, stroke, or tumor, but in most cases the cause is unknown. These do not involve an alteration of consciousness but may have observable motor components or may be a subjective sensory or emotional phenomenon.
- *Complex partial seizures:* Complex partial seizures are caused by a localized abnormal discharge, which leads to an impairment of consciousness. Complex partial seizures can occur in two ways. Simple partial seizures can develop into complex partial seizures, or consciousness can be impaired from the beginning. In complex partial seizures the abnormal discharges are most often localized in the temporal lobes.
- *Secondary generalization seizures:* In both simple and complex partial seizures the electrical discharges can spread to the entire brain. This is called a secondary generalization. This leads to the seizure ending with generalized convulsions and unconsciousness.

## FDA INDICATIONS

Epilepsy:

The vagal nerve stimulation system originally known as the NeuroCybernetic Prosthesis System, made by Cyberonics, of Houston, was approved by the FDA in July, 1997. The FDA approved the NeuroCybernetic Prosthesis for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over age 12 diagnosed with medically refractory partial onset seizures.[1]

Depression:

In July 2005, the FDA approved the NeuroCybernetic Prosthesis, VNS Therapy system for adjunctive long term treatment for chronic recurrent depression in patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. The approval letter allows the sponsor to begin commercial distribution of the VNS Therapy System for treatment resistant depression. [2]

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) [4]

***The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Review (MCR) document and provide the directive for all Medicare members. The directives from this MCR document may be followed if there are no available NCD or LCD documents available and outlined below.***

CMS has a National Coverage Determination (NCD) #160.18 for vagus nerve stimulation and covers VNS for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed".

CMS has also issued a decision memo #00313R for vagus nerve stimulation and does not cover VNS for the treatment of resistant depression.

## INITIAL COVERAGE CRITERIA [1 4 5-9 10-30 31-32]

Vagal Nerve Stimulation (VNS) may be considered ***medically necessary and may be authorized*** when **ALL** of the following criteria are met: [ALL]

- ❑ Age of 12 years or older; and
- ❑ Diagnosis of medically intractable partial onset seizures (e.g., 6 or more per month[7]) refractory or unresponsive to anti-epileptic medications and are not candidates for resective epileptic surgery (e.g., lesionectomy or medial temporal lobectomy), or have failed previous surgical treatment.
- ❑ Prescriber and physician administering the treatment is a Neurologist; and
- ❑ Duration of illness is two years (not required in acute-life threatening situations or if there is a focal cerebral lesion); and
- ❑ Drug resistant seizures persist despite an adequate trial of antiepileptic drugs (AEDs) defined as the failure of adequate trials of two tolerated, appropriately chosen and administered antiepileptic drugs (whether as monotherapy or in combination) to achieve seizure freedom.

**NOTES:**

- ❑ Controversy exists regarding the efficacy of VNS use in children under age 12. A small number of studies have demonstrated efficacy; however, these were noted to have small sample sizes from either uncontrolled prospective trials or retrospective analysis of chart data. The FDA continues to exclude children under age 12.
- ❑ Being unresponsive to a medication is defined as failing to get a 50% reduction in seizure frequency when taking the medication appropriately. For patients with occasional seizure events, reliable demonstration of a reduction in seizures can take some time statistically, at least 3 new events must be observed to establish an estimate of a new event rate.
- ❑ Assessing unresponsiveness must exclude pseudo-unresponsiveness due to poor compliance taking medication. Whenever possible drug levels in bloodstream should be tested and compared to therapeutic-level norms. Increases in visit frequency, more frequent blood-level checks, and sometimes observing the taking of medications may be needed to separate pseudo- from real unresponsiveness.
- ❑ Seizure control and drug-induced remission are most likely to occur within the first year of starting treatment

- Seizures that are drug resistant for two years or more are unlikely to go into spontaneous remission

## CONTINUATION OF THERAPY

Surgical implantation of a vagal nerve stimulator or VNS routinely takes place in an outpatient surgery setting or with an overnight inpatient stay if the medical condition warrants an overnight stay. The surgery is typically performed under general anesthesia.

## COVERAGE EXCLUSIONS [1 2 4 5]

VNS Therapy is excluded for any the following indications:

- Requests that do not meet all of the above outlined criteria.
- Children under the age of 12 years.
- Requests for VNS for any other condition other than medically intractable partial onset epileptic seizure disorder (e.g., headaches, bipolar disorders, anxiety, chronic refractory hiccups, obesity, autism, bulimia, Alzheimer's disease, essential tremors, and obsessive compulsive disorder).
- Diagnosed progressive metabolic or degenerative disorders that will result in continued deterioration within a 6 to 12 month time frame (e.g., malignant brain neoplasm or Rasmussen's encephalitis.)
- Previous bilateral or left cervical vagotomy is contraindicated
- Members with serious cardiovascular and/or respiratory conditions should be evaluated closely by a Neurologist or other appropriate specialist to determine if the member should be excluded
- Requests for VNS for treatment resistant depression or other mental health disorders.
- Shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy is contraindicated in patients implanted with a VNS Therapy System.

## SUMMARY OF MEDICAL EVIDENCE [10-30]

*VNS in the Management of Epilepsy*

The first case series of patients treated with vagus nerve stimulation (VNS) was reported in 1990. [16] This was followed by two large pivotal trials of VNS in patients with partial epilepsy, the E03 study and the E05 study. [17-21]

Two long term studies conducted in 2007 continued to report a seizure frequency reduction and severity up to 50 percent for a timeframe to four years post VNS implantation. The first study reported a 47 percent reduction in seizure severity and post-ictal period compared with a five month baseline pre-implantation over a six year period. The seizure reduction improved each year during the six year follow-up (e.g., 14%, 25%, 29%, 29%, 43% and 50%).[14] A second retrospective study reported a seizure reduction of 50% after mean follow up of 44 months. The mean number of seizures monthly pre-implantation were reported at 41 compared with 7 post implantation ($p<0.001$).[15]

Englot et al. (2011) performed the first meta-analysis of VNS efficacy in epilepsy, identifying 74 clinical studies with 3321 patients suffering from intractable epilepsy. These studies included 3 blinded, randomized controlled trials (Class I evidence); 2 nonblinded, randomized controlled trials (Class II evidence); 10 prospective studies (Class III evidence); and numerous retrospective studies. After VNS, seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after > 1 year of therapy. At the last follow-up, seizures were reduced by 50% or more in approximately 50% of the patients, and VNS predicted a ≥ 50% reduction in seizures with a main effects OR of 1.83 (95% CI 1.80-1.86). Patients with generalized epilepsy and children benefited significantly from VNS despite their exclusion from initial approval of the device. Furthermore, posttraumatic epilepsy and tuberous sclerosis were positive predictors of a favorable outcome. In conclusion, VNS is an effective and relatively safe adjunctive therapy in patients with medically refractory epilepsy not amenable to resection. However, it is important to recognize that complete seizure freedom is rarely achieved using VNS and that a quarter of patients do not receive any benefit from therapy. [29]

Connor et al. (2012) conducted a study to evaluate the published results of vagal nerve stimulation (VNS) for medically refractory seizures according to evidence-based criteria. The authors performed a review of available literature published between 1980 and 2010. Inclusion criteria for articles included more than 10 patient's evaluated, average follow-up of 1 or more years, inclusion of medically refractory epilepsy, and consistent preoperative surgical evaluation. Articles were divided into 4 classes of evidence according to criteria established by the American Academy of Neurology. A total of 70 publications were reviewed, of which 20 were selected for review based on inclusion and exclusion criteria. There were 2 articles that provided Class I evidence, 7 that met criteria for Class II evidence, and 11 that provided Class III evidence. The majority of evidence supports VNS usage in partial epilepsy with a seizure reduction of 50% or more in the majority of cases and freedom from seizure in 6%-27% of patients who responded to stimulation. High stimulation with a gradual increase in VNS stimulation over the first 6 weeks to 3 months postoperatively is well supported by Class I and II data. Predictors of positive response included absence of bilateral interictal epileptiform activity and cortical malformations. The authors concluded that vagal nerve stimulation is a safe and effective alternative for adult and pediatric populations with epilepsy refractory to medical and other surgical management. [28]

Klinkenberg et al. (2012) conducted a randomized controlled trial to evaluate the effects of vagus nerve stimulation (VNS) in children with intractable epilepsy on seizure frequency and severity and in terms of tolerability and safety. In this study 41 children (23 males; 18 females; mean age at implantation 11y 2mo, SD 4y 2mo, range 3y 10mo-17y 8mo) were included. Thirty-five participants had localization-related epilepsy (25 symptomatic; 10 cryptogenic), while six participants had generalized epilepsy (four symptomatic; two idiopathic). During a baseline period of 12 weeks, seizure frequency and severity were recorded using seizure diaries and the adapted Chalfont Seizure Severity Scale (NHS3), after which the participants entered a blinded active controlled phase of 20 weeks. During this phase, half of the participants received high-output VNS (maximally 1.75mA) and the other half received low-output stimulation (0.25mA). Finally, all participants received high-output stimulation for 19 weeks. For both phases, seizure frequency and severity were assessed as during the baseline period. At the end of the randomized controlled blinded phase, seizure frequency reduction

of 50% or more occurred in 16% of the high-output stimulation group and in 21% of the low-output stimulation group (p=1.00). There was no significant difference in the decrease in seizure severity between participants in the stimulation groups. Overall, VNS reduced seizure frequency by 50% or more in 26% of participants at the end of the add-on phase The overall seizure severity also improved (p<0.001). The authors concluded that VNS is a safe and well-tolerated adjunctive treatment of epilepsy in children. Our results suggest that the effect of VNS on seizure frequency in children is limited. However, the possible reduction in seizure severity and improvement in well-being makes this treatment worth considering in individual children with intractable epilepsy. [27]

*VNS in the Management of Depression*

A double-blind, parallel-group, randomized controlled study of VNS for TRD (n=235) (D02 trial) evaluated 235 patients with depressed bipolar disorder or major depressive disorder with a VNS activated 2 weeks following implantation. Only 222 of the 235 patients were evaluated with no documentation of reason for patient loss. A 10 week follow suggested 15 percent of active treatment and 10% of sham treatment had a response. Short term efficacy was not demonstrated.[11] A twelve month follow up on 205 of these patients was performed by the same authors. A 27 percent response rate and 15.8 percent remission rate were reported. The study was noted to be flawed due to concomitant use of antidepressants and treatment adjustments during the study and no comparative group. Thirty study enrollees had worsened depression which required hospitalization.[10]

A second study reported 24-month outcomes of the D02 study (Sackeim et al., 2007). The study defined those who had ≥ 50% improvement in HDRS24 scores at 3 months as "early responders," and those who met this criterion at 12 months, but not at 3 months, as "late responders." Based on this definition, 14.6% of patients were early responders, 19.5% were late responders, and 65.9% did not respond to the treatment. Overall, 63.3% who were early responders maintained the treatment benefit for 12 months and 76.7% were still responders at 24 months. Of the late responders, 65.0% were still responders at 24 months. However, the threshold level defining a successful response to the treatment was lowered to an improvement ≥ 40% rather than ≥ 50% in HDRS24 scores. Therefore, if the original threshold were used to evaluate the data, the rate for maintaining the treatment benefit would likely be lower. The mean changes in HDRS24 scores over the entire study period were significantly greater in early (54.7%) and in late (51.3%) responders, compared with patients who did not respond to the treatment (12.9%) (P<0.0001). This result indicates that the treatment effect may not be entirely attributed to a potential placebo effect. The long-term extension study was uncontrolled and unblinded in the true treatment; therefore, it is not possible to quantify the treatment benefit. [12]

A systematic review (2008) was performed evaluating the efficacy of VNS in treatment resistant depression. Data was reviewed from January 2000 through September 2007. Ninety-eight references were obtained but only 18 met the quality criteria and were included in the review. Only one double blind, randomized study was performed. The authors concluded, "in a majority of the preliminary open studies selected for this review, VNS was associated with a significant reduction of the depressive symptoms (primary outcome: Hamilton

Depression Rating Scale, HDRS) in the short and long term. This double-blind study gave rather inconclusive results. Generally, VNS is reported to be a safe and feasible procedure, despite its invasive nature. However, despite the promising results reported mainly in open studies, further clinical trials are needed to confirm its efficacy in major depression". [13]

The meta-analysis by Berry et al. (2013) pooled data from individual patients (n=1460) who had participated in 6 clinical studies and then performed a patient-level meta-analysis. The study included 1035 patients (mean age, 48 years; 66.2% women) receiving adjunct VNS and 425 patients (mean age, 49 years; 70% women) receiving treatment as usual. The study found that VNS improved the symptoms of depression and that remission rates were higher for adjunct VNS than in the TAU control group. VNS was associated with a greater likelihood of response based on ≥ 50% improvement on the MADRS scale (odds ratio [OR], 3.19; 95% confidence interval [CI], 2.12 to 4.66), remission based on MADRS scale (OR, 4.99; 95% CI, 2.93 to 7.76), and response based on CGI-I scale (OR, 7; 95% CI, 4.63 to 10.83), compared with TAU. However, because the study was largely based on data from patients who had participated in open-label trials, the benefit seen may have been caused by a placebo effect, which is likely to have biased the meta-analysis. [23]

The systematic review and meta-analysis by Martin and Martín-Sánchez (2012) included 9 studies (n=727 patients) in the meta-analysis and analyzed the effectiveness data separately based on study design. The authors reported that, while the open-label studies showed effectiveness (31.8% responders on HDRD scale, range 23.2% to 41.8%; P<0.001), the RCT found no statistically significant difference between VNS therapy and the sham VNS control (OR, 1.61; 95% CI, 0.72 to 3.62; P=0.25), further suggesting that the observed response might have been caused by a placebo effect. [24]

Aaronson et al. (2013) performed a multicenter, double blind study, 331 patients with TRD were randomized to one of three dose groups: LOW (0.25 mA current, 130 μs pulse width), MEDIUM (0.5-1.0 mA, 250 μs), or HIGH (1.25-1.5 mA, 250 μs). A highly treatment-resistant population (>97% had failed to respond to ≥6 previous treatments) was enrolled. Response and adverse effects were assessed for 22 weeks (end of acute phase), after which output current could be increased, if clinically warranted. Assessments then continued until Week 50 (end of long-term phase).The results showed that VNS therapy was well tolerated. During the acute phase, all groups showed statistically significant improvement on the primary efficacy endpoint (change in Inventory of Depressive Symptomatology-Clinician Administered Version [IDS-C]), but not for any between-treatment group comparisons. In the long-term phase, mean change in IDS-C scores showed continued improvement. Post-hoc analyses demonstrated a statistically significant correlation between total charge delivered per day and decreasing depressive symptoms; and analysis of acute phase responders demonstrated significantly greater durability of response at MEDIUM and HIGH doses than at the LOW dose. The authors concluded that TRD patients who received adjunctive VNS showed significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year. Higher electrical dose parameters were associated with response durability. [25]

*VNS for Other Conditions*

Vagus Nerve Stimulation has been used to treat patients with various other conditions such as those with headaches, bipolar disorders, anxiety, chronic refractory hiccups, obesity, autism, bulimia, Alzheimer's disease, essential tremors, and obsessive compulsive disorder. Only preliminary studies have been performed; findings need to be validated through large randomized controlled studies with long term outcomes before safety and efficacy can be established.

Professional Organizations [6-9]

*The American Academy of Neurology* evidence-based guideline on vagal nerve stimulation for the treatment of epilepsy (2013) indicates that VNS may be considered for seizures in children, for Lennox-Gastaut syndrome (LGS) associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C). Children should be carefully monitored for site infection after VNS implantation.

*The Institute for Clinical Systems Improvement (ICSI)* Adult Depression in Primary Care Guideline (2013) indicates that vagal nerve stimulation is approved by the FDA for treatment-resistant depression on the basis of its potential benefit with long-term use. The evidence primarily stems from open labeled uncontrolled trials. It is not indicated for use in the acute treatment phase, and it has been studied only in treatment-resistant depression.

*The California Technology Assessment Forum* (2011) Assessment on Vagal Nerve Stimulation for Treatment Resistant Depression indicates that the use of vagal nerve stimulation for treatment resistant depression does not meet CTAF Technology Assessment Criteria 3 through 5 for safety, effectiveness, and improvement in health outcomes.

*The National Institute for Health and Care Excellence (NICE) 2009* Guidance on Vagus nerve stimulation for treatment-resistant depression indicates that the current evidence on the safety and efficacy of vagus nerve stimulation (VNS) for treatment resistant depression is inadequate in quantity and quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research. It should be used only in patients with treatment-resistant depression.

**CODING INFORMATION:** THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

| CPT | Description |
|---|---|
| 61885 | Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array |
| 64553 | Percutaneous implantation of neurostimulator electrodes; cranial nerve |
| 64568 | Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator |

| | |
|---|---|
| 64569 | Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator |
| 64570 | Removal of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator |
| 95970 | Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming |
| 95974 | Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour |
| 95975 | Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, each additional 30 minutes after first hour (List separately in addition to code for primary procedure) |

| **HCPCS** | **Description** |
|---|---|
| L8679 | Implantable neurostimulator, pulse generator, any type |
| L8680 | Implantable neurostimulator electrode, each |
| L8681 | Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only |
| L8682 | Implantable neurostimulator radiofrequency receiver |
| L8683 | Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver |
| L8685 | Implantable neurostimulator pulse generator, single array, rechargeable, includes extension |
| L8686 | Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension |
| L8687 | Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension |
| L8688 | Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension |
| L8689 | External recharging system for battery (internal) for use with implantable neurostimulator, replacement only |

| **ICD-10** | **Description: [For dates of service on or after 10/01/2015]** |
|---|---|
| G40.001-G40.019 | Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable |
| G40.101-G40.119 | Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures |
| G40.201-G40.219 | Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures |
| G40.311-G40.319 | Generalized idiopathic epilepsy and epileptic syndromes |

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**Other Resources**

31. UpToDate: Rose, BD (ed), Waltham, MA. Updated 2019:
    - Schachter SC, Boon P. Vagus Nerve stimulation.
    - Wilfong A, Nordli DR, Pedley Ta. Overview of treatment of seizures and epileptic syndromes in children.
    - Schachter SC, Pedley TA, Wilterdink JL. Overview of the management of epilepsy in Adults.
    - Boggs J, Pedley TA Schmader KE. Et al. Treatment of Seizures and epilepsy in the elderly: Diagnosis and treatment.
    - Holtzheimer P. Unipolar depression in adults: Overview of neuromodulation procedures and Treatment with surgical approaches.
    - Sirven J. Evaluation and management of drug-resistant epilepsy.
32. Advanced Medical Review (AMR): Policy reviewed by a physician board certified Board certified in Neurology. 6/3/2014.

**Revision/Review History:** 3/8/18 & 6/19/19: Policy reviewed, no changes to criteria.