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Medical Policy Manual

Topic: Vagus Nerve Stimulation

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Section: Surgery

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Vagus nerve stimulation (VNS) involves implantation of an infraclavicular pulse generator that sends weak electric impulses to the left vagus nerve within the carotid sheath in the neck. The impulses are delivered via 2 electrodes connected to the generator and wrapped around the vagus nerve. The stimulator may be programmed in advance or may be activated on demand by placing a magnet against the generator implantation site. Recently, less-invasive, non-surgical means of transcutaneous VNS have been developed; however, these non-implantable methods have not yet received approval from the U.S. Food and Drug Administration (FDA) as a treatment for any condition. While the mechanisms for the therapeutic effects of vagal nerve stimulation 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.

Regulatory Status

Implantable VNS Devices

Several VNS therapy systems by Cyberonics Inc. have pre-market approval (PMA) from the U.S. Food and Drug Administration (FDA) for treatment of refractory partial-onset seizures and chronic or recurrent depression, when certain criteria are met. For example, in 1997, the NeuroCybernetic

Prosthesis (NCP®) system was approved for use in conjunction with drugs or surgery "as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures." The VNS Therapy™ System was approved in 2005 "for the adjunctive long-term treatment of chronic or recurrent depression for 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."

Non-Implantable VNS Devices

Cerbomed has developed a transcutaneous VNS (t-VNS®) system, NEMOS®, that uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Patients self-administer electric stimulation for several hours a day; no surgical procedure is required. The device has not been FDA approved for use in the US. In addition, Electrocore has developed a non-invasive VNS (gammaCore®) that is currently being investigated for headache; the device does not have FDA approval.

MEDICAL POLICY CRITERIA

I. Vagus nerve stimulation (VNS) may be considered **medically necessary** as a treatment of medically refractory seizures. Patients must have tried and been unresponsive to or intolerant of four antiepileptic drugs.

II. VNS is considered **investigational** for all other indications, including but not limited to the following:

A. Anxiety disorders

B. Bulimia

C. Chronic refractory hiccups

D. Cognitive impairment associated with Alzheimer's disease

E. Depression

F. Essential tremors

G. Fibromyalgia

H. Headaches

I. Heart failure

J. Obesity

K. Traumatic brain injury

L. Tinnitus

III. Non-implantable vagus nerve stimulation devices are considered **investigational** for all indications.

SCIENTIFIC EVIDENCE

In order to assess the safety and effectiveness of vagus nerve stimulation (VNS), particularly for indications in which the primary outcomes are subjective (e.g., pain reduction, improved mood, improved functioning), large, blinded, long-term, randomized controlled trials (RCTs) are necessary for the following reasons:

- Randomization

  Randomization helps to achieve equal distribution of individual differences (known and unknown, clinical and demographic) by randomly assigning patients to either active VNS, sham VNS, or standard medical treatment groups. Consequently, any observed differences in the outcome may, with reasonable assuredness, be attributed to the treatment under investigation.

- Appropriate control group

  A comparable sham and/or medical treatment control group helps control for placebo effects and any variable natural history of the condition being treated. These control groups also help in determining whether any treatment effect from VNS provides a significant advantage over placebo or standard treatment options.

- Blinding

  Blinding of study participants, caregivers, and investigators to the treatment assignments helps control for bias for or against the treatment. Blinding helps assure that placebo effects are not interpreted as true treatment effects.

- Large study population

  Large studies help ensure the ability to rule out chance as an explanation of study findings.

- Adequate follow-up

  Follow-up periods must be long enough to determine the durability of any treatment effects.

- Adverse event reporting

  Adverse effects related to complications from VNS must be considered in evaluating the net health impact of this technology.

Literature Appraisal

Medically Refractory Seizures

The criteria for VNS for seizures are based on a 1998 BlueCross BlueShield Association (BCBSA) Technology Evaluation Center (TEC) assessment[1], a 2010 updated Cochrane review[2] of the 2 published double-blind randomized controlled trials (RCTs)[3,4], and numerous case series, retrospective reviews, and other non-randomized studies on adult[5-10], pediatric,[11-18] or mixed[19-24] patient populations. Both reviews concluded that VNS reduced seizure frequency in patients with drug resistant partial-onset seizures.

The 2 RCTs were large, well-designed multicenter trials that reported an approximate 25% reduction in partial-onset seizure frequency following 3 months of VNS. Adverse effects were mild and consisted primarily of hoarseness or voice change during "on" periods of stimulation. The remaining literature is limited to numerous non-randomized trials. Although evidence from non-randomized studies are generally considered unreliable for assessing the safety and effectiveness of VNS, the findings from these numerous studies have consistently shown significantly reduced seizure activity in patients with drug-resistant epilepsy. In addition, clinical practice guidelines from the American Academy of Neurology stated that "…sufficient evidence exists to rank VNS for epilepsy as effective and safe…"[25] Thus, despite the lack of RCTs in the published clinical evidence, VNS has become a recognized standard of care for treatment in selected patients with medically refractory seizures.

Refractory Depression

Technology Assessment

A 2006 BCBSA TEC Assessment[26], evaluated the effectiveness of VNS in the treatment of refractory depression compared with continued medical management. The evidence consisted of one case series, one observational study, and one randomized controlled trial. The assessment found that "overall, the evidence supporting efficacy of VNS is not strong."

- The randomized controlled trial (RCT) of 221 patients that compared VNS with a sham control (implanted but inactivated VNS) did not show a statistically significant difference between VNS and continued medical therapy in relieving depression symptoms.[27-29] The trial was short and possibly underpowered to detect a smaller amount of VNS benefit. In addition the adequacy of blinding was questionable.
- The observational study included a subset of 205 VNS treated patients from the RCT described above who were followed long-term. A separately recruited control group of 124 patients received ongoing treatment for depression.[27,30] Although the study findings favored the VNS therapy group, this evidence is considered unreliable due to significant methodological limitations including but not limited to the following:
    - Non-randomized allocation of treatment does not control for possible between-group differences in individual patient characteristics; thus, it cannot be ruled out that these differences, rather than the treatments received, were responsible for the observed outcomes.
    - The lack of a sham study group does not control for the expected placebo effects.
    - The inadequate, non-concurrent comparison group does not permit conclusions on the efficacy of VNS compared with placebo or other treatment options.
    - The differences in sites of care between VNS treated patients and controls may introduce response bias. (Analysis performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness.)

    - Differences in concomitant therapy changes cannot be ruled out as an explanation of the observed outcomes.
- The case series (Study D-01) was a feasibility study of 60 patients receiving VNS; improvement was reported in depression scores.[31] It is uncertain whether loss to follow-up was addressed adequately in the analysis. In addition, the case series is limited by the lack of an appropriate comparison group.

Systematic Reviews and Meta-analysis

- In a meta-analysis that included 14 studies, Martin and Martin-Sanchez reported that among the uncontrolled studies in their analysis, 31.8% of subjects responded to VNS treatment.[32] However, results from a meta-regression to predict each study's effect size suggested that 84% of the observed variation across studies was explained by baseline depression severity ($p<0.0001$). The authors concluded that current data was insufficient to determine whether VNS is an effective treatment for depression and noted that positive results from uncontrolled studies may be due to placebo effect.
- A 2008 systematic review and meta-analysis for VNS of treatment-resistant depression identified no new RCTs since the pivotal RCT described above, which the authors determined to be inconclusive.[33] As noted above, RCTs are considered the appropriate design for studying VNS for any indication. However, this review also included 17 nonrandomized, open studies which found VNS to be associated with a reduction in depressive symptoms. The authors concluded that, while open studies have reported promising results, further clinical trials are needed to study the mechanism of action and cost-effectiveness, and to confirm the efficacy of VNS in treatment-resistant depression.

Randomized Controlled Trials (RCT)

Since the BCBSA TEC Assessment and the 2008 systematic review, a single randomized controlled trial was identified that evaluated the effectiveness of VNS for treatment of refractory depression. Aaronson et al. randomized 331 patients with treatment-resistant depression (TRD) into one of three VNS 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).[32] Patients were included that had a history of failure to respond to at least 4 adequate dose/duration of antidepressant treatment trials from at least 2 different treatment categories. After 22 weeks, the current dose could be adjusted in any of the groups. At follow up visits at weeks 10, 14, 18, and 22 after enrollment, there was no statistically significant difference between the dose groups for the study's primary outcome, defined as a change in the Inventory of Depressive Symptomatology (IDS) score from baseline. However, the mean IDS score improved significantly for each of the groups from baseline to the 22 week follow up. At 50 weeks of follow up, there were no significant differences between the treatment dose groups for any of the depression scores used. Most patients completed the study; however, there was a high rate of reported adverse events, including voice alteration in 72.2%, dyspnea in 32.3%, and pain in 31.7%. Interpretation of the IDS improvement over time is limited by the lack of a no treatment control group. Approximately 20% of the patients included had a history of bipolar disorder; and therefore, the results may not be representative of most patients with treatment resistant unipolar depression. The lack of a placebo comparison group within this study limits conclusions regarding the isolated treatment effect of VNS in this patient population.

Non-randomized Trials

Numerous non-randomized studies evaluated the effectiveness of VNS for the treatment of refractory depression.[31,33-39] It is not possible to reach reliable conclusions from these studies as they fail to control for the biases discussed above.

Other Indications

Randomized Controlled Trials (RCT)

No randomized controlled trials evaluated the effectiveness of VNS for the treatment of indications other than seizures and depression.

Non-randomized Trials

Small case series ($n \leq 40$ patients) and one non-randomized comparison study described experiences with VNS in patients with bulimia , anxiety, Alzheimer's disease[40], migraine headaches[41,42], obesity, heart failure[43,44], essential tremor[45], and eating disorders including obesity and food cravings[46]. For the reasons noted above, evidence from non-randomized studies is considered unreliable in the study of VNS as a treatment for any indication.

Adverse Effects

The most commonly reported adverse effects of VNS have been mild and consist primarily of hoarseness of voice during "on" periods of stimulation, transient throat pain, and coughing. More serious adverse events reported include, but are not limited to:[1,27,33,47-50]

- direct delivery of the current to the nerve due to generator malfunction
- modified synchronization between cardiac and respiratory activity affecting the oxygen delivery to tissues
- heart block with ventricular standstill
- bradyarrhythmias and severe asystolia
- changes in respiration during sleep.

Non-Implantable Vagus Nerve Stimulators

Randomized Controlled Trials (RCTs)

Hein et al., reported on 37 depression patients included in two randomized sham controlled add-on studies on auricular transcutaneous electric nerve stimulation.[51] Patients were stimulated 5 times a week on a daily basis for two weeks. The Beck Depression Inventory (BDI) and Hamilton Depression Rating Scales (HAMD) were administered at baseline and at the end of the 2 week treatment period. A statistically significant improvement in BDI scores was observed the stimulation group compared to the sham group. HAMD scores did not significantly differ between groups. Authors called for additional randomized trials with larger sample size to confirm study results.

Non-randomized Trials

Two small case series were identified that used a transcutaneous stimulator (t-VNS device) for treatment of medication refractory seizures. In a small case series of 10 patients with treatment resistant epilepsy, Stefan et al. reported that 3 patients withdrew from the study, while 5/7 patients reported a reduction in seizure frequency.[52] In another small case series, He et al. reported that among 14 pediatric patients with intractable epilepsy who were treated with bilateral t-VNS stimulation, of the 13 patients who completed follow up, mean reduction in self-reported seizure frequency was 31.8% after 8 weeks, 54.1% from week 9 to 16, and 54.2% from week 17 to 24.[53] For the reasons noted above, evidence from non-

randomized studies is considered unreliable in the study of non-implantable VNS as a treatment for any indication.

Clinical Practice Guidelines

American Psychiatric Association (APA)[54]

In 2010, the APA made recommendations regarding the use of vagus nerve stimulation (VNS) for patients with major depressive disorder. Strategies to address nonresponse during an acute phase of depression include the following:

- 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).
- Maintenance treatment with vagus nerve stimulation is also appropriate for individuals whose symptoms have responded to this treatment modality.

These recommendations are not based upon "clinical confidence" or evidence, but upon expert opinion.

American Academy of Neurology (AAN)[55]

The AAN released an updated consensus statement in 2013 that stated, "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*)."

*Level C evidence was defined as the following: "Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population."

Summary

Although the current evidence is limited, vagus nerve stimulation (VNS) has evolved to a standard of care as a treatment of medically refractory seizures. Therefore, VNS for medically refractory seizures may be considered medically necessary for patients who have had inadequate response to or are intolerant of at least 4 antiepileptic drugs.

Due to the lack of reliable data the evidence is insufficient to permit conclusions about the benefit of VNS in the treatment of any other condition. Therefore, VNS is considered investigational for all indications other than selected patients with refractory seizures.

The evidence is insufficient to permit conclusions regarding the efficacy of transcutaneous vagus nerve stimulation (tVNS) as a treatment for any condition. In addition, no tVNS devices have received approval from the U.S. Food and Drug Administration (FDA). Therefore, transcutaneous vagus nerve stimulation is considered investigational as a treatment for all indications.

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CROSS REFERENCES

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy, Surgery, Policy No. 16

CODES	NUMBER	DESCRIPTION
CPT	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 two or more electrode arrays
	61888	Revision or removal of cranial neurostimulator pulse generator or receiver
	64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
	64568	Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
	64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
	64570	Removal of cranial nerve (e.g., 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 (ie, cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming
	95971	; simple spinal cord, or peripheral (ie, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter,

CODES	NUMBER	DESCRIPTION
		with intraoperative or subsequent programming
	95974	Electronic analysis of implanted neurostimulator pulse generator system (e.g., 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	; 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)
	0312T	Vagus nerve blocking therapy (morbid obesity); laparoscopic implantation of neurostimulator electrode array, anterior and posterior vagal trunks adjacent to esophagogastric junction (EGJ), with implantation of pulse generator, includes programming
	0313T	Vagus nerve blocking therapy (morbid obesity); laparoscopic revision or replacement of vagal trunk neurostimulator electrode array, including connection to existing pulse generator
	0314T	Vagus nerve blocking therapy (morbid obesity); laparoscopic removal of vagal trunk neurostimulator electrode array and pulse generator
	0315T	Vagus nerve blocking therapy (morbid obesity); removal of pulse generator
	0316T	Vagus nerve blocking therapy (morbid obesity); replacement of pulse generator
	0317T	Vagus nerve blocking therapy (morbid obesity); neurostimulator pulse generator electronic analysis, includes reprogramming when performed
HCPCS	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

CODES	NUMBER	DESCRIPTION
	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