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. 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

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

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.
depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.”

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

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**
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.

- 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.[^32] 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, no new randomized controlled trials evaluating the effectiveness of VNS for treatment of refractory depression have been published.

**Non-randomized Trials**
Numerous non-randomized studies evaluated the effectiveness of VNS for the treatment of refractory depression.\textsuperscript{[31-38]} 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 ≤ 40 patients) and one non-randomized comparison study described experiences with VNS in patients with bulimia, anxiety, Alzheimer’s disease\textsuperscript{[39]}, migraine headaches\textsuperscript{[40,41]}, obesity, heart failure\textsuperscript{[42,43]}, essential tremor\textsuperscript{[44]}, and eating disorders including obesity and food cravings\textsuperscript{[45]}. 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:\textsuperscript{[1,27,32,46-49]}

- 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.

Clinical Practice Guidelines

American Psychiatric Association (APA)\textsuperscript{[50]}

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.

Summary
Vagus nerve stimulation (VNS) has evolved to a standard of care as a treatment of medically refractory seizures based on 2 randomized, controlled trials that reported a significant reduction in seizure frequency, and a large number of nonrandomized studies that have consistently confirmed those results. 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, long-term evidence from well designed randomized, controlled trials, 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.

REFERENCES


29. U.S. Food and Drug Administration Center for Devices and Radiological Health. Executive Summary and Discussion of the Vagus Nerve Stimulation (VNS) Therapy Depression Indication Clinical Data (Updated to Include Information from Deficiency Letter Response). [cited 05/02/2012]; Available from: [http://www.fda.gov/ohrms/dockets/ac/04/briefing/4047b1_01_Clinical%20Executive%20Summery-FINAL.htm](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4047b1_01_Clinical%20Executive%20Summery-FINAL.htm)


**CROSS REFERENCES**

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

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