

Health Technology Clinical Committee Findings and Coverage Decision

Topic: **Vagal Nerve Stimulation for Epilepsy and Depression**

Meeting Date: **August 28, 2009**

Final Adoption: **October 30th, 2009**

Number and Coverage Topic

20090828A – Vagal Nerve Stimulation: Vagal Nerve Stimulation (VNS) for the treatment of Epilepsy and Depression.

HTCC Coverage Determination

Vagal Nerve Stimulation for the treatment of Epilepsy is a **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination.

Vagal Nerve Stimulation for the treatment of Depression is a **non-covered benefit**.

HTCC Reimbursement Determination

❖ **Limitations of Coverage**

Vagal Nerve Stimulation are conditionally covered, for management of epileptic seizures in patients twelve years of age or older that have a medically refractory seizure disorder.

❖ **Non-Covered Indicators**

Vagal Nerve Stimulation for the treatment of depression.

❖ **Agency Contact Information**

Agency	Contact Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-762-6004
Health and Recovery Services Administration	1-800-562-3022

Health Technology Background

The Vagal Nerve Stimulation topic was selected and published in December 2008 to undergo an evidence review process. VNS first was clinically applied as an anti-convulsant in 1980s and is now being explored for disease beyond epilepsy, including depression. Epilepsy is a neurological condition impacting 2.3 million people in the US, with an estimated 600,000 experiencing complex partial seizures. Epilepsy causes seizures that can involve loss of consciousness and may not be controlled by medication. Depression (major depressive disorder) is a mood disorder that affects approximately 18.8 million adults in the US annually. Depression has a high recurrence rate and associated burden, interfering with ability to work, sleep, eat and function, with symptoms from persistent sadness or anxiety to suicide. The etiology of depression is unclear, and it appears that a variety of genetic, environmental and psychological factors may be involved in the onset of a depressive period. VNS stimulated the left vagus nerve using electrical signals generated by an implanted pulse generator. The vagus nerve carries sensory information to the brain from the head, neck, thorax and abdomen. Evolving understanding continues on the neurobiological effects of VNS therapy as a function of the different use parameters (frequency, intensity, pulse width, duration and dose). Exact mechanism of action by which VNS reduces clinical symptoms is not known, but imaging and clinical studies demonstrate brain function changes.

One of several forms of therapeutic physical brain stimulation (both invasive and non-invasive) includes: electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). Alternative treatments include: pharmacotherapy and brain surgery.

VNS has been used as an adjunct treatment for epilepsy (most continue with medication) in patients 12 years of age or older, who continue to suffer from partial-onset seizures, generally with: a seizure frequency of at least six per month while on antiepileptic medication, and who have either failed surgical treatment or are not suitable surgical candidates. VNS was recently approved as an adjunct to treat major treatment resistant depression in persons over 18 years of age. VNS potential advantages: treatment expectations with VNS are a reduction of frequency and severity and length of seizures or depressive episodes. VNS potential disadvantages: changing the stimulation parameters reverses many minor complications such as voice changes while others are permanent or may require device explantation. VNS may increase depression and suicide ideation and suicide attempts.

In July 2009, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed, Vagal Nerve Stimulation report is 123 pages, and identified a relatively large amount of literature.

- The VNS report for Epilepsy identified one meta-analysis (Privitera, 2002), and 39 primary studies. The primary studies consisted of data from 2 RCTs, four non-RCTs, and 22 uncontrolled studies. The body of evidence reviewed involved studies with 13 to 454 patients, as well as registry data for 4,743 patients with medically refractory epilepsy syndromes and one retrospective analysis involving 1,819 patients of the incidence of sudden death in epilepsy (SUDEP).

- The VNS report for Depression did not identify a meta-analysis that met the criteria for review. The majority of the available evidence regarding the safety and efficacy of VNS for treatment-resistant depression comes from studies funded by or performed in collaboration with Cyberonics (2009) in patient groups ranging from 9 to 235. Overall, the manufacturer planned and/or executed six studies, although, to date, complete data sets have not been published for all of the studies. The search of the peer-reviewed literature identified the following controlled studies: one double-blind, randomized, parallel-group, sham-controlled study; one post hoc comparative analysis; one nonrandomized comparison study; and one small, prospective, open-label study. The remaining evidence was from five uncontrolled studies. There were two articles reporting on the prospective, uncontrolled extensions of the RCT. There were six articles reporting data from one open-label, nonrandomized, uncontrolled clinical study. One study reported on the results of a prospective, open-label, single-arm study. Finally, the evidence also included one small, prospective, open-label, single-arm pilot study of VNS for chronic treatment-resistant depression; and one prospective, open-label, single-arm study investigating VNS in patients with rapid cycling bipolar disorder.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other presented information shows it is safe, effective and has value. The committee met on August 28th, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at <http://www.hta.hca.wa.gov> under the committee section.

Committee Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The committee concludes that the best available evidence on vagus nerve stimulators has been collected and summarized. The evidence is comprehensive and robust:

- Vagal Nerve Stimulation – Epilepsy. The evidence based technology assessment report identified a relatively large amount of literature. The reviews and studies selected for this detailed review included one meta-analysis (Privitera, 2002), and 39 primary studies. The primary studies consisted of data from two randomized trials, four nonrandomized controlled trials, and 33 uncontrolled studies. The body of evidence reviewed involved studies with 13 to 454 patients, as well as registry data for 4,743 patients with medically refractory epilepsy syndromes and one retrospective analysis involving 1,819 patients of the incidence of sudden death in epilepsy (SUDEP).
- Vagal Nerve Stimulation – Depression. The evidence based technology assessment report did not identify a meta-analysis that met the criteria for review. The majority of the available evidence regarding the safety and efficacy of VNS for treatment-resistant depression comes from studies funded by or performed in

collaboration with Cyberonics (2009) in patient groups ranging from 9 to 235. Overall, the manufacturer planned and/or executed six studies, although, to date, complete data sets have not been published for all of the studies. The search of the peer-reviewed literature identified the following controlled studies: one double-blind, randomized, parallel-group, sham-controlled study; one post hoc comparative analysis; one nonrandomized comparison study; and one small, prospective, open-label study. The remaining evidence was from five uncontrolled studies. There were two articles reporting on the prospective, uncontrolled extensions of the RCT. There were six articles reporting data from one open-label, nonrandomized, uncontrolled clinical study. One study reported on the results of a prospective, open-label, single-arm study. Finally, the evidence also included one small, prospective, open-label, single-arm pilot study of VNS for chronic treatment-resistant depression; and one prospective, open-label, single-arm study investigating VNS in patients with rapid cycling bipolar disorder.

2. Is the technology safe?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- Mortality – the evidence based technology assessment report indicated little evidence of increased mortality.
 - Specific to epilepsy, no evidence that VNS increases incidence of Sudden Unexpected Death in Epilepsy, rates from one cohort study of overall death were 4.1 per 1000 for VNS patients and 4.5 per 1000 in cohort.
 - Specific to depression, evidence is more limited, and the one RCT reported one death due to suicide in VNS group. Worsening of depression and attempted suicides occurred, but evidence does not yet correlate to VNS use; data more short term (2 year).
- Morbidity - the evidence based technology assessment report indicated data on complications related to epilepsy were available up to ten years and depression up to two years. Most common complications were mild including: voice alterations, hoarseness, cough, pain, dyspnea, infection, paresthesia, headache, and pharyngitis. Additional complications reported related to treatment for depression included: attempted suicide, suicide ideation, worsening of depression, manic episodes, agitation, hypomania, and cardiovascular events.
 - Committee identified dyspnea as potentially more significant concern, with the evidence based technology assessment reporting one RCT rate of dsypnea at 25% in VNS group.
- The evidence based technology assessment report indicated that evidence for pediatric patients demonstrated similar adverse effects, though the evidence base is small, pilot studies and follow up length is not as long.

3. Is the technology effective?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

- Epilepsy – Reduction in severity or frequency of seizure is the primary outcome measured. The treatment does not cure or eliminate seizures, though one comparator -surgical treatment’s goal is to eliminate seizures.
 - Effect of VNS on Seizure Control in Partial Epilepsy – two randomized placebo controlled trials (n=312) reduced seizure frequency by 25% from baseline compared with 6.1% to 15.2% in sham VNS. Sample size and use of sham treatment (low pulse) strengthened results as VNS can be felt. Overall, 21% to 75% of patients experienced at least a 50% mean reduction. Treatment benefit was maintained for up to 10 years.
 - One prospective study is available for generalized Seizures and Lennox-Gastaut Syndrome (n=78) – the limited evidence suggests VNS therapy may be effective for these types of seizures, but the quality of the evidence was poor. Controlled studies are needed to confirm results.
 - Insufficient evidence related to population characteristics, but small pilot studies of patients under 12 and older than 50 with no previous surgical treatment may be responsive to VNS; those with higher baseline seizure and who were older with onset of seizures may benefit more.

- Depression – Reduction in severity or frequency of depressive episodes is the primary outcome measured. The evidence based technology assessment report indicates one randomized control trial with 235 patients and a placebo lasting 12 weeks did not demonstrate a statistically significant difference.
 - Treatment is potentially investigated for chronic, severe, treatment resistant major depression disorder or bipolar disorder. Definition is not uniformly defined in literature.
 - The evidence based technology assessment report also provided information on the different instruments to measure changes in depression, and indicating a threshold of more than 50% change over baseline generally considered clinically meaningful; however the final scores must also be taken into account as changes can be misleading if the final scores still fall below the threshold for severe depression. Additionally, comparators varied in studies and may confound results, especially if comparator treatments changed during study.
 - Limited uncontrolled trials produced conflicting results compared to standard treatment and had substantial limitations beyond study design in that significant heterogeneity among comparison groups was not adjusted for in one study, and a lower than originally defined threshold for “responders” was adopted in a second study.
 - All studies were industry sponsored or supported.

- Quality of Life: The evidence based technology report included quality of life as a key outcome.
 - Epilepsy related quality of life data is of moderate level with inconsistent results which may be due to insufficient power to detect difference.
 - Depression related quality of life data was not separately reported from the depression rating scales.

4. Is the technology cost-effective?

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective.

Summary of committee considerations follows.

- Epilepsy – the technology assessment report indicated that several small European studies conclude VNS could be cost-effective by reduction in unplanned hospital and other treatment costs by average of \$3000 per patient (N= 20 and 19 patients).
- Depression – the technology assessment report included two economic evaluations; however, when efficacy has not been proven, economic evaluations cannot substantiate cost-effectiveness.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

5. Evidence availability and technology features

The committee concludes that the best available evidence on vagus nerve stimulators has been collected and summarized. The evidence is comprehensive and robust:

- Evidence from meta-analysis and several well designed randomized, controlled trials, with adequate participants, appropriate controls or alternative(s), and patient centered outcomes were available for epilepsy treatment.
- Patients with medically refractory epilepsy who are unsuccessful or non-surgical candidates have few treatment alternatives and face difficult and sometimes severe complications from the disease.
- Evidence from one controlled trial and several other trials is available on VNS for medically refractory depression; a condition that has serious impacts and few additional treatment options.

6. Is it safe?

The committee concludes that the comprehensive evidence reviewed shows that the VNS technology is safe compared with alternative management for epilepsy and unproven compared to alternative management for depression. Key factors to the committee's conclusion included:

- Mortality – the committee agreed with the evidence report conclusions that indicated little evidence of increased mortality generally, but remain concerned with the suicide death reported in the VNS treatment group related to depression and overall more limited evidence and follow up length in studies for depression treatment.
- Morbidity - the committee generally agreed with the evidence report conclusions that most adverse effects were mild, especially in comparison with epilepsy condition specifically, and based on explanation or voluntary termination could be addressed.

- Committee identified dyspnea as potentially more significant concern, with the evidence based technology assessment reporting one RCT rate of dsypnea at 25% in VNS group.
- Committee discussed rate of explantation or voluntary termination (not well reported) in relation to harms because the device can be removed or turned off to alleviate some complications thus limiting the magnitude of adverse effect, and as factor or proxy for how severe complications might be (group voluntarily discontinued).
- The committee found evidence insufficient on safety for use in pediatric (under 12) given the very small and limited evidence base identified in the evidence report and discussed this as a larger concern given the limited ability to generalize to children, and the potential for serious complications.

7. Is it effective?

The committee concludes that the comprehensive evidence reviewed shows that VNS is proven more effective for treatment of medically refractory epilepsy and unproven from treatment of depression:

- For Epilepsy – the measure of reduction in severity or frequency of seizure is an important, patient centered, and appropriate measure of effectiveness. The committee agreed that evidence indicated VNS was effective in reducing severity or frequency of seizures in patients with medically refractory epilepsy.
- For Depression – the committee agreed that an appropriate measure would be the reduction in frequency or duration of major depressive episodes in patients with medically refractory depression, and concluded that the current best evidence (one RCT) does not currently demonstrate an improvement in this measure. Additional high quality evidence is needed.

8. Is it cost-effective?

The Committee concludes that the comprehensive evidence review shows that VNS is equally or more cost effective for epilepsy and unproven for depression.

- Epilepsy – Committee agreed that limited data existed; however, several studies did show that VNS treatment to be cost-effective due to the reduction in seizures that necessitated medical treatment. Committee agreed that long term, good quality evidence would be desirable, but is not available. Committee agreed that no evidence in the report displayed any evidence to say otherwise.
- Depression – Committee agreed that primarily where evidence of effectiveness has not yet been shown, cost-effectiveness cannot be shown, and the cost studies available for VNS treatment of depression are low quality.

9. Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee discussed multiple other factors that were important for consideration in their overall decision. Summary of committee considerations follows.

- Epilepsy special populations - age: Committee agreed that the data presented in both the technology evidence report and what the FDA as approved, that VNS treatment is effective for those 12 years of age or older for epilepsy treatment. Committee discussed VNS treatment for those patients under the age of 12; however, the committee agreed that not enough data exists on safety and efficacy

for children less than 12 years of age and current IRB approved trials should be utilized to access treatment while assessing benefit.

10. Medicare Decision and Expert Treatment Guidelines

Committee reviewed and discussed the Medicare coverage decision and expert guidelines as identified and reported in the technology assessment report.

Epilepsy –

- Centers for Medicare and Medicaid Services (1999) – there is a national coverage decision (NCD) relating to Vagal Nerve Stimulators for Epilepsy. The NCD states that VNS is reasonable and necessary for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed.
- Guidelines – three guidelines were stated in the technology assessment evidence report, those included: (1) MSAC, Australia, 2008, VNS is reasonably safe in context of the condition being treated but insufficient evidence of effectiveness and net benefit of VNS for patients with medically refractory epilepsy; (2) Clinical Evidence: British Medical Journal Review, 2009, reported high level VNS may reduce seizure frequency in people with partial seizures that are refractory to medication, complications and long term effect unknown; and (3) NICE, 2004, VNS indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and adults who are refractory to antiepileptic medication and who are not suitable candidates for resective surgery. VNS is indicated for patients with epileptic disorder with predominantly partial seizures, with or without secondary generalized epilepsy, and generalized epilepsy.

Depression –

- Centers for Medicare and Medicaid Services (2007) – there is a national coverage decision (NCD) relating to Vagal Nerve Stimulators for Depression. The NCD states that VNS is not reasonable and necessary for resistant depression (not covered).
- Guidelines – three guidelines were included in the technology assessment evidence report, those included: (1) CTAF, 2006, concluded that VNS for depression does not meet criteria four and five for effectiveness and improvement of health outcomes in treatment resistant depression; (2) ISCI, 2009, concluded that quality of evidence currently does not meet ICSI's threshold for recommendation; and (3) Kaiser Permanente Care Management, 2006, concluded insufficient evidence to recommend VNS.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, input from a clinical expert, and agency and state utilization information. The committee concluded that the current evidence on Vagal Nerve Stimulators demonstrates that there is sufficient evidence to cover the use of Vagal Nerve Stimulators for Epilepsy, but not cover the use of Vagal Nerve Stimulators for Depression. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. The committee found that Vagal Nerve Stimulators for Epilepsy didn't have a significant mortality rate; serious morbidity

from VNS was unusual; and VNS was effective in reducing severity or frequency of seizures. The committee found that Vagal Nerve Stimulators were proven to be more effective for patients 12 years and older.

Epilepsy – Based on these findings, the committee unanimously voted 9 to 0 to cover Vagal Nerve Stimulation, with conditions: limited Vagal Nerve Stimulation for management of epileptic seizures for patients with 12 years of age or older that have a medically refractory seizure disorder.

Depression – Based on these findings, the committee unanimously voted 9 to 0 for no coverage of Vagal Nerve Stimulation for the treatment of depression.

Health Technology Clinical Committee Authority

Washington State's legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, through its Health Technology Assessment program to engage in a process for evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages. Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC), determines how selected health technologies are covered by several state agencies. RCW 70.14.080-140. These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases their decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.