



Draft

VAGUS NERVE STIMULATION FOR  
DEPRESSION

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**Produced by:**  
The Health Resources Commission  
Office for Oregon Health Policy & Research

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### **Health Resources Commission**

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

### ***Overview***

In 2007 the Oregon Health Resources Commission (HRC) appointed a technology subcommittee to perform evidence-based reviews of medical technologies. Members of the subcommittee for this review consisted of five physicians, and an attorney who serves as the consumer representative. All meetings were held in public with appropriate notice provided. The technologies chosen for review are chosen by the HRC which takes into account stakeholder input when deciding on topics to consider. The HRC utilizes source documents from sources previously approved by the Commission. In conducting the review process and working with our source providers the HRC defines the patient populations of interest, technologies to be studied and outcome measures for analysis,

considering both effectiveness and safety. Evidence is specifically sought for subgroups of patients based on race, ethnicity and age, demographics. Using standardized methods, the Center for Evidence based policy's contractor (Hayes Inc.) review systematic databases, and the medical literature. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The Center for Evidence Based Policy's report, "Vagus Nerve Stimulation for Depression, August 2009", was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony. This report does not recite or characterize all the evidence that was discussed by the source documents, the subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

David Pass, MD

Director, Health Resources Commission

Office for Oregon Health Policy & Research

1225 Ferry St. SE

Salem, Oregon 97301

Phone: 503-373-1779

Fax: 503-378-5511

Email: [HRC.info@state.or.us](mailto:HRC.info@state.or.us)

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There will be a charge for copying and handling in providing hard copy documents from the Office of Oregon Health Policy & Research.

### ***Critical Policy***

*Health Resources Commission*

- "Clinical outcomes are the most important indicators of comparative effectiveness"
- "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

### ***Clinical Overview***

Vagus nerve stimulation (VNS) is a therapy for treatment-resistant major depression and bipolar disorder in which electrical pulses are delivered to the cervical portion of the

vagus nerve by an implanted generator, called a neurocybernetic prosthesis. The goal of VNS is to reduce the severity and/or duration of a depressive period.

Depression is a mood disorder that affects approximately 18.8 million adults in the United States annually. Treatment depends on the type and severity of depression. Milder forms of depression are initially treated with psychotherapy. Moderate to severe depression is often treated with a combined approach of antidepressants and psychotherapy. Electroconvulsive therapy (ECT) is an alternative treatment for severe and life-threatening depression (major depression, bipolar disorder) or for patients who cannot take or do not respond to antidepressant medication. Individuals with chronic, severe depression who have failed to respond to multiple courses of antidepressants have been labeled “treatment resistant” but this is not a formal diagnostic category in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) manual. Chronic intermittent electrical stimulation of the left vagus nerve, originally designed as a treatment for medically refractory epilepsy, has been introduced as an adjunctive therapy for treatment-resistant major depression and bipolar disorder. The VNS system consists of an implantable pulse generator and lead and an external programming system used to change stimulation settings.

VNS has been introduced as an adjunct to antidepressant treatment in patients with severe, chronic MDD or bipolar disorder who have not responded to several trials of medications. In the brain, the vagus nerve forms connections with the medulla; most connections are to the nucleus tractus solitarius (NTS). The NTS is connected to a wide range of nerve projections from and to other areas of the brain. Among these, the vagus nerve is the primary sensory organ of the NTS.

The term “vagus nerve stimulation” generally relates to electrical stimulation of the left vagus nerve at the cervical level. Left VNS is preferred to right VNS since the heart rate is mostly influenced by the right vagus nerve and stimulation could induce cardiovascular complications. VNS was first introduced to treat medically refractory seizures (FDA, 2009a; Goodnick, Rush, George, Marangell, & Sackeim, 2001; Kosel & Schlaepfer, 2003; Schachter & Saper, 1998). The rationale for its use as an antiseizure treatment was based on the observation that stimulation of the vagus nerve could alter electric brain activity in animals. This led to the theory that synchronous epileptic discharges could be interrupted or prevented by stimulation of the vagus nerve. Investigators observed improved mood and cognition in epilepsy patients who received VNS. In addition, other observations were felt to indicate that VNS may be effective for the treatment of depression, these include:

- Antiepileptic drugs are effective in the treatment of mood disorders.
- Positron emission tomography (PET) studies demonstrate that VNS affects metabolism and thus function of limbic structures that suggest an antidepressant effect.
- VNS modulates concentrations of monoamines within the central nervous system.
- An anatomic connection exists between the vagus nerve and brain structures related to mood disorders.

*Mechanism of Action:*

The exact mechanism of action by which VNS may reduce the symptoms of depression is yet unknown, but it has been shown that VNS has an effect on brain metabolism and brain function (Carpenter et al., 2004; Cunningham, Mifflin, Gould, & Frazer, 2008; Faingold, 2008; Follasa et al., 2007; Groves & Brown, 2005; Henry, 2002; Kosel &

Schlaepfer, 2002; Lomarev et al., 2002; Mu et al., 2004; Pardo et al., 2008; Park, Goldman, Carpenter, Price, & Friehs, 2007; Ressler & Mayberg, 2007; Theodore, 2004; Trivedi, 2003).

The potential population of patients with “difficult-to-treat” or “treatment-resistant” depression where VNS might be used is estimated to be 200,000.

In July 2005, the Food and Drug Administration (FDA) approved the NeuroCybernetic Prosthesis (NCP)<sup>®</sup> System, also called the VNS Therapy<sup>™</sup> System (Cyberonics Inc.), for adjunctive long-term treatment of chronic or recurrent depression in patients 18 years of age or older who are experiencing a major antidepressant episode and have not had an adequate response to four or more adequate antidepressant treatments. (Cyberonics, 2007; FDA, 2005a).

### ***Quality of the Evidence***

For quality of evidence the Med project and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration.

The quality of selected primary studies was assessed with the aid of MED checklists for RCTs and cohort studies. These checklists are adapted from similar checklists used by the National Institute for Health and Clinical Excellence (NICE, 2009a) and Scottish Intercollegiate Guidelines Network (SIGN, 2009). Overall bodies of evidence by outcome and indication were graded as “high,” “moderate,” or “low” quality according to the GRADE system (Atkins et al., 2004; Guyatt et al., 2008).

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; data from a number of these studies were presented to the Food and Drug Administration (FDA) to support the Premarket Approval (PMA) application. Overall, the manufacturer planned and/or executed six studies, designated D01 to D06, although, to date, complete data sets have not been published for all of the studies.

### ***Weighing the Evidence***

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee’s task was to evaluate

### ***Scope and Key Questions***

This report focuses on evidence investigating VNS as an adjunct to medical treatment in adult patients with “treatment-resistant” major depression or bipolar disorder.

Comparator treatments are medical treatment, psychotherapy, and electroconvulsive therapy. Clinically important outcome measures include changes in depression severity (remission of depression and  $\geq 50\%$  reduction in severity), quality of life, function, and complications. Additional outcome measures include whether VNS reduced the duration of depression-related hospitalization and the number of psychiatric treatments.

**Key Questions:**

1. *Is the use of vagus nerve stimulators with or without antidepressant medication effective, compared with medication alone, in reducing the severity of depression, or in improving function or quality of life?*
2. *Are vagus nerve stimulators safe?*
3. *Does effectiveness vary by age, response to antidepressants, or other patient characteristics?*

**Conclusions:***Limitations of the Evidence:*

1. Other than one fair quality RCT all of the effectiveness/efficacy studies were of poor quality.
2. Lack of controls, small sample sizes, and the short follow-up in the controlled study limited the evidence for safety assessments.
3. There was a lack of studies investigating predictors for a positive treatment benefit.
4. The quality of the overall body of evidence is poor.

*Conclusions**Effectiveness:*

1. One fair quality RCT failed to demonstrate any difference between VNS treated groups and sham VNS treated groups on any specified primary outcome.
2. There is insufficient evidence to conclude that VNS improves depression, quality of life, and function in patients with treatment-resistant MDD and bipolar disorders.

*Harms*

1. Serious harms have been reported with VNS for depression.
2. There is insufficient evidence to determine if VNS may increase depression, suicidal ideation and suicide attempts.

*Subgroups*

1. There is insufficient evidence to determine a comparative difference between groups based on diagnosis (MDD vs. Bipolar disorder). No data was found which addressed differences for age, gender or disease severity.

**Supporting Evidence:**

Key Question 1. *Is the use of vagus nerve stimulators with or without antidepressant medication effective, compared with medication alone, in reducing the severity of depression, or in improving function or quality of life?*

*Evidence from RCTs:*

The highest level of evidence was derived from one 12-week randomized, double-blind, controlled study (RCT). In this study, active VNS (n=112) with an implantable device was compared with sham VNS (n=110) with an identical device that was not turned on. Active VNS was no more effective than sham VNS in alleviating symptoms of depression among a population of adults diagnosed with MDD or bipolar disorder (type I

or II) who were experiencing a chronic, major depressive episode (MDE) despite multiple regimens of standard treatments. At week 12, there was no significant difference between active and sham VNS in treatment response rates (15.2% versus 10.0%, respectively;  $P=0.251$ ), nor were there significant differences between active and sham VNS groups for four of five scales used as secondary measures of efficacy. The only endpoint to show a significant difference between the two study arms was the self-administered IDS-SR.

*Evidence from Nonrandomized Controlled or Comparative Studies:*

The evidence from a nonrandomized comparative study was conflicting. The study reported a comparative analysis of outcomes between patients enrolled in the D02 long-term phase and another population of patients who were recruited for a separate study on healthcare costs associated with treatment-resistant depression; this latter study was not originally designed to be a control arm for the D02 study, thus lowering the overall quality of the study. This study is referred to as the D04 study. In this combined analysis, the primary endpoint was change over time in the patient-administered IDS-SR. For this endpoint, VNS and concomitant “treatment as usual” (VNS+TAU) was associated with significantly greater improvements than TAU alone during the full 12 months.

Compared with TAU, VNS+TAU was also associated with significant improvement in average change in HDRS scores over 12 months. For the entire study sample, 27% of VNS+TAU patients were responders compared with 15% of TAU patients ( $P=0.011$ ). However, there are several methodological flaws in these findings, including the underlying premise of using a convenience population as a standard for comparison. While the two nonrandomized study populations have similar baseline characteristics; there were significant differences between the two groups in severity of and history of depression, race, and use of certain concomitant therapies. Moreover, when FDA analysts evaluated data limited to patients recruited from the same sites, only one outcome measure (average change in IDS-SR, 12-month data) remained significantly different between the VNS and the TAU groups. Using this restricted data set, 16.5% of the VNS group and 11.0% of the TAU group were responders; this difference was no longer statistically significant ( $P=0.27$ ).

In one small, nonrandomized controlled study; VNS significantly improved depression, assessed with HDRS28, decreased the length of depression-related hospitalization from 65 to 44 days, and decreased the number of psychiatric treatments per year from 33 to 14. There was no significant change in these parameters for the control group.

*Evidence from Uncontrolled Studies:*

The remaining studies were prospective uncontrolled studies. Overall, VNS improved depression versus baseline across studies but response rates were low. Function and quality of life also improved. The longest follow-up was available for the D01 and D02 studies. A second study reported on the 24-month outcomes of the D01 and D02 studies. The study defined those that had  $\geq 50\%$  improvements in HDRS24 scores at 3 months as “early responders” and those that met this criterion at 12 months, but not at 3 months, as “late responders.” Based on this definition, 30.5% of patients in the D01 (D02, 14.6%) were early responders, 23.7% (D02, 19.5%) were late responders, and 45.8% (D02, 65.9%) did not respond to the treatment. Overall, in the D01 study, 72.2% (D02, 63.3%)

who were early responders maintained the treatment benefit for 12 months, and 61.1% were still responders at 24 months. Of the late responders, 78.8% (D02, 65.0%) were still responders at 24 months. The mean changes in HDRS24 scores over the entire study period were significantly greater in early (D01, 61.6%; D02, 54.7%) and in late responders (D01, 60.8%; D02, 51.3%) compared with patients who did not respond to the treatment (D01, 24.5%; D02, 12.9%) ( $P < 0.0001$ ). The long-term extension studies were uncontrolled and unblinded, and, therefore, it is not possible to quantify the true treatment benefit. Furthermore, the threshold level defining a successful response to the treatment was lowered to an improvement of  $\geq 40\%$  rather than  $\geq 50\%$  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.

#### Key Question 2: *Are vagus nerve stimulators safe?*

There were limited data from controlled trials available for VNS therapy in depression. In the RCT (D02 trial,  $n=235$ ), device explantation due to infection was necessary in one patient in the active VNS group and one suicide occurred, also in the active VNS group. Other adverse events were similar for both groups. In the clinical studies, patients experienced the following complications that may have been related to VNS or electrode implantation: general pain, specific pain (incision-site, chest, neck, ear), headache, abnormal wound healing, edema, infection, pharyngitis, dyspnea, coughing, dysphagia, dyspepsia, nausea, tooth disorder, dizziness, twitching, insomnia, rash, palpitations, and generalized spasms. The prevalence of reported adverse events varies and was not reported in all studies. In the RCT, the prevalence of complications was as follows (% patients, VNS group, sham control group): voice alteration (68%, 38%); cough increased (29%, 9%); dyspnea (23%, 14%); dysphagia (21%, 11%); neck pain (21%, 10%), paresthesia (16%, 10%); vomiting (11%, 5%); laryngismus (11%, 2%); dyspepsia (10%, 5%); wound infection (8%, 2%); palpitations (5%, 3%). Three of 235 patients withdrew from the study due to the serious complications.

Some complications noted across studies were serious and/or required hospitalization, including: suicide, attempted suicide, and suicide ideation; worsening of depression; manic episodes; agitation; hypomania; central nervous system (CNS) toxicity; asystole; bradycardia; syncope; venous thrombophlebitis; nephrolithiasis; cholelithiasis; and pulmonary embolism. While adjusting the stimulation parameters reversed some complications, such as voice alterations, other complications (e.g., dyspnea, pain) required treatment or were permanent. Several cardiovascular events occurred that might have been related to VNS therapy. One death of unknown cause occurred in the D02 study. Long-term safety data are not currently available from prospective controlled studies, although 2-year data from the uncontrolled studies indicated that most serious adverse events usually occurred shortly after implantation of the device, and complication rates did not appear to increase over time. In one 2-year follow-up, patients experienced voice alterations (27%), dyspnea (8%), and neck pain (13%).

#### Key Question 3: *Does effectiveness vary by age, response to antidepressants, or other patient characteristics?*

Nierenberg, Alpert, Gardner-Schuster, Seay, & Mischoulon (2008) compared outcomes for unipolar versus bipolar disorder for a 12 months time frame using data from the open-label, uncontrolled extension of the RCT. Only 13 patients (11%) who participated in this study had bipolar disorder, and 104 patients had unipolar depression. The study compared changes in symptoms of depression (HDRS24, ISD-SR30), physical and mental functioning (MOS-36), and episodes of mania and hypermania (YMRS) between these two patient groups. Patients with unipolar and bipolar depression experienced similar improvements in these parameters, with no statistically significant difference for any of the instruments used to assess these outcomes. While this result indicates that patients with unipolar depression and those with bipolar disorder experience similar results with VNS, the sample size was too small to detect a difference in these outcome measures.

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