Washington State Health Care Authority

Health Technology Assessment

HTA Final Report
Vagus Nerve Stimulation for Epilepsy

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Vagus Nerve Stimulation for Epilepsy

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VAGUS NERVE STIMULATION (VNS) FOR EPILEPSY

PURPOSE OF THE TECHNOLOGY

Vagus nerve stimulation (VNS) is a treatment for epilepsy 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 frequency and severity of seizures in patients with seizures that are refractory to medication.

EXECUTIVE SUMMARY

Clinical Overview

Approximately 2.3 million people in the United States have epilepsy. It has been estimated that approximately 600,000 people experience complex partial seizures, i.e., seizures that involve loss of consciousness and which cannot be controlled by treatment with the currently available antiepileptic drugs. These are known as medically refractory seizures. It has been estimated that 33% of patients with epilepsy have inadequate seizure control. Resective brain surgery can be effective in some patients with medically refractory seizures; however, seizure surgery carries significant risk and may not be a viable option for many patients.

Chronic intermittent electrical stimulation of the left vagus nerve has been introduced as a treatment for intractable partial epilepsy. The NeuroCybernetic Prosthesis® (NCP) System (Cyberonics Inc.) includes a pulse generator and a lead designed to deliver physician-programmed stimulation to the vagus nerve. The device, implanted subcutaneously into the upper chest, delivers pulses of current via electrodes attached to the left vagus nerve in the neck.

Policy Context

Vagus nerve stimulation (VNS) is a topic of interest to members of the Oregon Health & Science University Medicaid Evidence-based Decision (OHSU MED) collaboration and the Washington State Health Care Authority (HSA). Accordingly, VNS for epilepsy is one of seven health technologies selected by the Washington State Health Care Authority (HCA) for review in 2009 (HCA, 2008). VNS is indicated as a treatment for epilepsy in patients 12 years of age or older, who suffer from partial-onset seizures, 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. Issues of interest for

this update include additional evidence regarding younger patients, patients with other types of seizures and epileptic syndromes, and long-term safety.

Scope

This report focuses on the use of VNS for the treatment of medically refractory epilepsy. VNS is generally compared with sham VNS, with an implanted device that is turned off or set to low stimulation. VNS is also compared with medical treatment and surgical resection. Clinical trials evaluated the effect of VNS of seizure frequency, quality of life (QOL), and complications.

Methods

Evidence evaluated for this report was obtained from a search of the peer-reviewed literature, spanning 1985 to June 2009. Thirty-seven primary studies and one meta-analysis reporting on VNS therapy for medically refractory epilepsy were selected for detailed review for this evaluation. The evidence consisted of data from two randomized trials, four nonrandomized controlled trials, and 31 uncontrolled studies. Most of the early evidence regarding the safety and efficacy of VNS comes from studies funded by or performed in collaboration with Cyberonics Inc.; data from 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 E01 to E05, and an open-label, uncontrolled extension study (XE5).

The quality of the selected primary studies was assessed with the aid of MED checklists for randomized controlled trials (RCTs) and cohort studies and was graded as “good,” “fair,” or “poor.” Overall bodies of evidence by outcome and indication were graded as “high,” “moderate,” or “low” quality according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Findings

The body of evidence reviewed involved studies with 13 to 454 patients, as well as registry data for 4743 patients with medically refractory epilepsy syndromes and one retrospective study involving 1819 patients reporting rates of sudden unexpected death in epilepsy (SUDEP) in patients receiving VNS. All of the studies used the NeuroCybernetic Prosthesis (NCP) System (Cyberonics Inc.) to deliver VNS. Most patients had partial seizures with or without secondary generalized seizures; less evidence was available for patients with generalized seizures, Lennox-Gastaut seizures, or other epileptic syndromes. In the studies evaluating VNS in patients with medically intractable epilepsy, the term “medically intractable” was generally used for patients who experienced at least

six seizures per month while taking antiepileptic medications. Several studies also involved individuals with surgically intractable seizures; these patients did not have epileptogenic foci amenable to resection or had undergone unsuccessful surgical procedures to control their epilepsy. These studies performed VNS using the NCP System, also referred to as the VNS Therapy System. Change in seizure frequency was the most commonly used outcome measure. The studies described reduction in seizure frequency mostly as percentage (percentage reduction in seizure frequency), or as mean (the average reduction in numbers of seizures) and median (the middle of a range of values). Patients who experienced greater than 50% seizure reduction were often referred to as responders. Complications and QOL were also assessed.

1. Is the use of vagus nerve stimulators plus antiepileptic medication effective, compared with medication alone, in reducing the frequency, duration, or severity of clinical seizures or in improving quality of life?

Evidence from the reviewed clinical trials indicated that VNS may reduce seizure frequency and improve QOL in some patients with medically intractable epilepsy, without the negative sedative and cognitive effects associated with most antiepileptic drugs. The majority of the evidence focused on patients with partial seizures who were older than 12 years of age. The evidence was limited for patients with other epileptic syndromes, with generalized epilepsy and Lennox-Gastaut syndrome (LGS) being the most common. The degree of improvement reported in the clinical trials was approximately 20% to 75% of patients experiencing at least a 50% mean reduction in seizure frequency compared with pretreatment baseline values; only a few patients became seizure free. These rates may not reflect the true size of the treatment effect of VNS since the placebo effect and response to concurrent pharmacologic therapy confounded the interpretation of the study results; therefore, the actual benefit of VNS may be lower. A number of studies evaluated the effect of VNS on QOL in patients with epileptic syndromes. The results of long-term studies indicated that the improvement in seizure frequency seen in some patients was sustained and may increase over time. Long-term efficacy studies demonstrated that efficacy persisted for up to 10 years. The results showed that VNS may improve elements of QOL in some patients but the extent and type of improvements were inconsistent among studies. While VNS improved QOL in several studies, in others, especially in studies with very small sample size, improvements were not significant or were noted in only one or two domains. At the present time, VNS is indicated only for patients who are 12 years of age or older with partial epilepsy that cannot be controlled with appropriate levels of antiepileptic medication. Current evidence also suggests that younger children may equally benefit from the treatment. A low level of evidence exists, suggesting that VNS may be effective in reducing seizure frequency in patients with generalized seizures, LGS, and other epilepsy syndromes. These studies had several design limitations, and additional evidence is needed to confirm these conclusions.

2. Are vagus nerve stimulators safe?

Safety data for VNS are available for a time frame of up to 10 years, with data from randomized controlled studies available for a time frame of 14 weeks. Overall, with few exceptions, complication rates were similar for sham VNS and active VNS in both studies. In the E03 trial, hoarseness/voice changes occurred in significantly more patients receiving the active treatment (37.3%) compared with sham VNS (13.3%). In the E05 study, in the active VNS group, statistically significant higher rates were observed for voice alterations (66.3%) and dyspnea (25.3%) versus the sham VNS group (30.1% and 10.7%, respectively). Patients in the sham VNS group also received stimulation, although at a much lower frequency. It is, therefore, possible that some or all complications are related to VNS but that only voice alterations and dyspnea were more pronounced with higher stimulation settings. Studies that compared the incidence of definite/probable sudden unexpected death in epilepsy (SUDEP) with the expected baseline rate for epilepsy revealed no increased risk of mortality that could be attributed to the use of VNS devices. Microwave transmissions, cellular phones, and airport systems do not seem to affect the VNS therapy generator or electrode leads. However, the manufacturer issued a safety alert in August 2001, advising against the use of shortwave, microwave, or therapeutic ultrasound diathermy for persons implanted with the NCP generator. No injuries have been reported to date, but diathermy may potentially cause the generator or leads to heat up and damage tissue, causing pain and discomfort. The safety of VNS during pregnancy has not been established.

3. Does effectiveness vary by age group, response to antiepileptics, or other patient characteristics?

There is a low level of evidence evaluating effectiveness by patient characteristics. The current low quality of evidence from small pilot studies suggests that VNS is equally effective in all age groups. VNS may be more effective for patients who had no previous surgical treatment for epilepsy. Predictors of a treatment response have not been established. Labar, Murphy, & Tecoma (1999) observed that patients with higher baseline seizure frequency and those who were older at epilepsy onset were more responsive to VNS therapy. The evidence is insufficient to define specific treatment guidelines regarding these patient characteristics, and additional research is required to substantiate these findings.

Conclusions and Discussion

There is high-quality evidence from randomized controlled trials, comparing high stimulation with a low-stimulation placebo VNS, and long-term studies regarding the benefit and safety of VNS to conclude that VNS reduces seizure rates in some patients older than 12 years of age with medically refractory partial-onset

seizures who are not suitable candidates for surgery or in whom surgical treatment has failed. There is low-quality evidence suggesting that in some cases, VNS may improve QOL in some patients. The improvements were, however, not consistent across studies. Evidence is of low quality for efficacy of VNS for children younger than 12 years of age, for generalized epilepsy, and for LGS. Study selection criteria were often broad, studies had small sample sizes and included several types of epilepsies and seizure types; thus, it was not possible to discern which patient subgroups were most likely to benefit from VNS treatment. Although, the results from these studies consistently indicated that VNS may be safe for pediatric populations and VNS may be as effective in children as it is in adults, additional evidence from good quality, randomized, controlled studies are needed to confirm these findings.

In clinical practice, patients with chronic, severe, medication-resistant epilepsy have few treatment options. VNS has been available in the United States for over 10 years for the treatment of partial seizures in patients older than 12 years of age whose seizures are not adequately controlled with antiepileptic seizures. Not all patients respond to VNS treatment and the treatment response may vary considerably among patients. Specific predictors of a positive treatment response have not been defined. However, low-quality evidence exists suggesting that those who had previously undergone antiepileptic surgery may benefit less from VNS. It is also important to note that response rates seem to increase over time. However, there is only low-quality evidence supporting this statement. Finally, it is important to carefully consider the risks of VNS versus epilepsy surgery and the benefits that can be obtained with both procedures. Currently, there are not enough studies directly comparing VNS with epilepsy surgery to guide the physician when making this choice.

BACKGROUND

Clinical Overview

Epilepsy is a neurological condition characterized by recurrent, unprovoked seizures. Epilepsy can be the result of injury, infections, structural abnormalities in the brain, abnormal fetal brain development, or exposure to toxic agents. However, in many patients, the cause is unknown. Recent studies have indicated that heredity plays an important role in epilepsy, with as many as 500 genes involved (Gardiner & Lehesjoki, 2000; NINDS, 2009; Phillips, 1997).

Epileptic seizures result from the simultaneous electrical discharge of groups of nerve cells in the brain. These epileptiform discharges may occur in a localized area of the brain, resulting in a partial seizure, or may involve nerve cells throughout the brain, causing a generalized seizure. Approximately 60% of patients with epilepsy experience partial seizures. These seizures are often described by the area of the brain from which they originate (e.g., temporal lobe seizures). There are two types of partial seizures:

- Simple partial seizures: The person remains conscious but may experience unusual feelings or sensations. These may be unexplained emotions such as anger or sadness, or the person may perceive smells, sounds, and tastes that are not actually present.
- Complex partial seizures: The person has a change in or loss of consciousness. A sign of complex partial seizures are altered states, dreamlike experiences, and repetitive behaviors such as blinks or twitches.

Generalized seizures are a result of widespread abnormal neuronal activity of the brain. The characteristics of different kinds of generalized seizures include:

- Absence seizures: Staring into space and/or jerking, twitching muscles.
- Tonic seizures: Stiffening of the muscles, involving mostly muscles in the back, legs, and arms.
- Clonic seizures: Repeated jerking movements of muscles on both sides of the body.
- Myoclonic seizures: Jerks or twitches of muscles in the upper body, arms, or legs.
- Atonic seizures: Sudden loss of normal muscle tone leading to falls or involuntary nodding of the head.
- Tonic-clonic seizures: A mixture of symptoms, including stiffening of the body and repeated jerks of the arms and/or legs, as well as loss of consciousness.

People may also experience several types of seizures that cannot be easily ascribed to these groups. There are many types of epilepsies, each with a set of characteristic symptoms. One prevalent type of epilepsy in children is Lennox-Gastaut syndrome (LGS), which is characterized by severe epilepsy with different kinds of seizures (NINDS, 2009).

The two major risks associated with epilepsy are status epilepticus and sudden unexpected death in epilepsy (SUDEP). Status epilepticus is a severe, life-threatening condition in which a person either has prolonged seizures, lasting 10 minutes or longer, or does not fully regain consciousness between seizures. Patients in status epilepticus require instant medical care. In SUDEP, patients with epilepsy have twice as high a risk of dying suddenly for no discernible medical reason. The cause for this increased risk is not yet known. Patients with poorly controlled epilepsy are also at increased risk of dying as a consequence of seizures or accidents, and they suffer from significant psychosocial problems such as education, employment, and quality of life (QOL) issues.

Approximately 2.3 million people in the United States have epilepsy. It has been estimated that approximately 600,000 people experience complex partial seizures, i.e., seizures that involve loss of consciousness and cannot be controlled by treatment with the currently available antiepileptic drugs. These are known as medically refractory seizures. It has been estimated that 33% of patients with epilepsy have inadequate seizure control. Resective brain surgery can be effective in some patients with medically refractory seizures; however, seizure surgery carries significant risk and may not be a viable option for many patients (Epilepsy Foundation, 2009; Guberman, 2004; Marks & Garcia, 1998; Uthman, Wilder, Hammond, & Reid, 1990; Uthman et al., 1993).

Observation that stimulation of the vagus nerve could alter electric brain activity in animals led to the theory that synchronous epileptic discharges could be interrupted or prevented by stimulation of the vagus nerve. After initial animal studies, pilot studies were conducted to evaluate the effect of vagus nerve stimulation (VNS) on people with intractable partial seizures. These initial human studies were successful in reducing seizure frequencies and resulted in further clinical trials. This research resulted in the 1997 approval by the Food and Drug Administration (FDA) of a device called a neurocybernetic prosthesis (NCP), an implantable generator that provides intermittent electrical stimulation to the cervical portion of the vagus nerve for chronic intermittent VNS (FDA, 2009). During the past 10 years, studies have attempted to elucidate the precise mechanism of action for VNS therapy.

The vagus nerve is the tenth and longest cranial nerve. Its name is derived from the Latin word “vagus,” meaning “wandering,” and it is so called due to the complex path it takes through the body from the brainstem through organs in the neck, thorax, and abdomen. The vagus nerve innervates vital structures in the body such as the heart, intestines, esophagus, stomach, liver, and muscles of

vocalization. In the brain, the vagus nerve forms connections with the medulla. Of these, the connection with the nucleus tractus solitarius (NTS) is regarded as pivotal to understanding the possible mechanism of the therapeutic effect of VNS for epilepsy. 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. It is also capable of processing extensive information. It is through the NTS that the vagus nerve gains access to centers in the brain that have been related to the generation of seizures such as the amygdala, hippocampus, entorhinal cortex—a part of the limbic system that most often generates complex partial seizures (Henry, 2002).

Policy Context

Vagus nerve stimulation (VNS) is a topic of interest to members of the Oregon Health & Science University Medicaid Evidence-based Decision (OHSU MED) collaboration and the Washington State Health Care Authority (HSA). Accordingly, VNS for epilepsy is one of seven health technologies selected by the Washington State Health Care Authority (HCA) for review in 2009 (HCA, 2008). VNS is indicated as a treatment for epilepsy in patients 12 years of age or older, who suffer from partial-onset seizures, 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. Issues of interest for this update include additional evidence regarding younger patients, patients with other types of seizures and epileptic syndromes, and long-term safety.

In July 1997, the NCP System was approved by the FDA (FDA, 2009).

In 1999, the Centers for Medicare & Medicaid Services (CMS) issued a National Coverage Determination (NCD) allowing Medicare coverage of VNS devices for patients with medically refractory partial-onset seizures, for whom surgery is not recommended or has failed. VNS is not covered for patients with other types of seizure disorders that are medically refractory and for whom surgery is not recommended or for whom surgery has failed (CMS, 2009).

Scope

- Population(s): Adults and children with medically intractable epilepsy
- Intervention(s): VNS as an adjunct to medical treatment
- Comparator(s): Sham-VNS, antiepileptic medication, surgical resection
- Outcome(s): Seizure severity, duration, frequency; quality of life; complications

Key Questions

1. *Is the use of vagus nerve stimulators plus antiepileptic medication effective, compared with medication alone, in reducing the frequency or severity of clinical seizures or in improving quality of life?*
2. *Are vagus nerve stimulators safe?*
3. *Does effectiveness vary by age group, response to antiepileptics, or other patient characteristics?*

TECHNOLOGY DESCRIPTION

The only device currently approved by the Food and Drug Administration (FDA) for vagus nerve stimulation (VNS), the NeuroCybernetic Prosthesis (NCP) System (Cyberonics Inc.), consists of a programmable generator that is implanted subcutaneously into the patient's chest and delivers pulses of current via electrodes attached to the vagus nerve in the left side of the neck. The stimulus is delivered periodically as a charge-balanced, biphasic, constant current pulse. The stimulation settings are tailored to individual patient tolerance. The most commonly studied stimulation paradigm has been a 20- to 30-Hertz (Hz), 1.0- to 2.0-milliampere (mA), 500-microsecond (μsec) pulse width with 30 seconds on and 5 minutes off, 24 hours per day. Safety features prevent sudden or excessive bursts of current. The intensity, width, and frequency of the electrical pulse can be adjusted, and telemetry data regarding the operating characteristics of the pulse generator can be retrieved with a programming wand using software run on a personal computer. Patients also have control of the stimulator by means of a magnet (Model 200 VNS Therapy Magnets), which can be worn on the wrist like a bracelet or watch, or clipped onto a belt or pants. When the patient senses the onset of a seizure, holding the magnet near the device for one to two seconds activates the stimulator. If there is discomfort or if the device is malfunctioning, stimulation can be stopped by placing the magnet over the vagus nerve stimulator permanently. The stimulator will resume as soon as the magnet is removed (Cyberonics, 2009). Microwaves or airport security systems do not affect the stimulator; however, strong electromagnetic fields may cause the device to activate. Implantation of the NCP System takes approximately 1 hour and can be performed under general or local anesthesia (Reid, 1990; Schachter & Saper, 1998; Terry, Tarver, & Zabara, 1990). The NCP System is available in two models: the VNS Therapy™ Pulse Models 102 and 102R generators. Model 101 is no longer distributed; a handheld computer is available to allow for faster programming sessions (Cyberonics, 2009).

Charous et al. (2001) cautioned that left-sided VNS may cause severe airway impairment in patients with undiagnosed right-sided vocal cord paralysis or with any partially obstructing laryngeal lesion (Charous, Kempster, Manders, & Ristanovic, 2001). The authors recommended a laryngeal examination prior to VNS implantation to avoid exacerbating a preexisting laryngeal pathology.

Washington State Data

Data from two Washington State Agencies were provided by the Health Technology Assessment Program. HTA coordinates the collection of any relevant agency utilization data.

Vagus Nerve Stimulation (VNS) is a selected topic. VNS uses a stimulator that sends electric impulses to the left vagus nerve in the neck via a lead implanted under the skin. VNS affects blood flow to different parts of the brain and affect neurotransmitters. VNS implantation is usually done as an outpatient procedure.

Estimates for costs and utilization from the Uniform Medical Plan and Washington State's Medicaid program are presented below in Table A. They provide an estimate of base costs and may not include all costs for Vagal Nerve Stimulation procedures and treatments. Information on relevant procedure and diagnostic codes is included after the result tables.

Table A:

Total* Payments for Vagus Nerve Stimulators

UMP & Medicaid Only | 2003-2008

	2003	2004	2005	2006	2007	2008	Total
Epilepsy	$74,053	$312,322	$276,473	$371,855	$510,892	$407,164	**$1,952,758**
Depression	$12,514	$0	$0	$7,426	$1,020	$1,240	**$22,200**
Total	$86,567	$312,322	$276,473	$379,281	$511,912	$408,404	**$1,974,958**

* Total includes inpatient, outpatient, implantations, revisions, removals, analysis, and medical devices. Total does not include physician services for assessment and maintenance and other costs that are not identifiable specific to the device.

Implantation Procedures by Condition

UMP & Medicaid Only | 2003-2008

Condition	Total
Epilepsy (345.41, 345.51, 780.39)	82
Epilepsy (345.xx, excluding above)	52
Depression (296.xx, 311)	4
Total	**138**

Implantation Procedures

UMP & Medicaid Only | 2003 - 2008

Procedure Code	Total
64553 (percutaneous implantation of neuroelectrodes)	2
64573 (incision for implantation of neuroelectrodes – cranial nerve)	136
Total	**138**

Procedure Codes

ICD9 Operation Codes

04.92 – Implantation or replacement of peripheral neurostimulator lead(s)
04.93 – Removal of peripheral neurostimulator lead(s) (coded with 86.05)
86.94 – Insertion or replacement of single array neurostimulator pulse generator, not specified as rechargeable
86.95 – Insertion or replacement of dual array neurostimulator pulse generator, not specified as rechargeable
86.96 – Insertion or replacement of other neurostimulator pulse generator
86.97 – Insertion or replacement of single array rechargeable neurostimulator pulse generator

86.98 – Insertion or replacement of dual array rechargeable neurostimulator pulse generator

CPT Codes
61885 – Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886 – Two or more arrays
61888 – Revision or removal of cranial neurostimulator pulse generator or receiver
64553 – Percutaneous implantation of neurostimulator electrodes; cranial nerve
64573 – Incision for implantation of neurostimulator electrodes; cranial nerve
95970 – Electronic analysis of implanted neurostimulator pulse generator system; simple or complex brain, spinal cord, or peripheral neurostimulator pulse generator/transmitter, without reprogramming
95974 – Complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour
95975 – Each additional 30 minutes

HCPCS Codes
C1767, 1778
L8680, L8681, L8682, L8683, L8685, L8686, L8687, L8688, and L8689

ICD-9 Diagnosis Codes
ICD-9-CM Diagnosis 345.11
Generalized convulsive epilepsy with intractable epilepsy

ICD-9-CM Diagnosis 345.41
Partial epilepsy with intractable epilepsy

ICD-9-CM Diagnosis 345.51
Partial epilepsy without impairment of consciousness with intractable epilepsy

ICD-9-CM Diagnosis 345.61
Infantile spasms with intractable epilepsy

ICD-9-CM Diagnosis 345.71
Epilepsia partialis continua with intractable epilepsy

ICD-9-CM Diagnosis 345.81
Other forms of epilepsy with intractable epilepsy

ICD-9-CM Diagnosis 345.91
Epilepsy unspecified with intractable epilepsy

ICD-9-CM Diagnosis 780.39
Other convulsions

METHODS

Search Strategy and Study Selection Criteria

This report uses evidence based on a search of the PreMEDLINE, MEDLINE, EMBASE, HealthSTAR, Current Contents, and Cochrane Library databases, spanning 1985 to 2007 and an additional search of MEDLINE and EMBASE from 2007 to June 2009. Search terms included *vagus nerve stimulation*, *vagal stimulation*, or *VNS* as keywords, subject words, abstract words, and title words, combined with *epilepsy* or *seizure*. The search was limited to English-language studies of human participants. Additional information was obtained from the Food and Drug Administration (FDA), the Epilepsy Foundation, Cyberonics Inc., the American Epilepsy Society (AES), and the National Institute of Neurological Disorders and Stroke (NINDS).

In general, prospective studies involving < 10 patients and retrospective studies were excluded from detailed review and analysis. Exceptions were made for studies involving special patient populations for which no randomized, placebo-controlled study reports were available. Examples are efficacy pilot trials of vagus nerve stimulation (VNS) for pediatric patients and older populations, patients with Lennox-Gastaut syndrome (LGS), and patients with generalized epilepsy. In these cases, retrospective analyses involving > 50 patients were included.

Inclusion Criteria: This rapid review selected peer-reviewed medical articles meeting the following criteria:

- Population(s): Adults and children with medically intractable epilepsy
- Intervention(s): VNS as an adjunct to medical treatment
- Comparator(s): Sham-VNS, antiepileptic medication, surgical resection
- Outcome(s): Seizure severity, duration, frequency; quality of life; complications

Additional selection criteria included: (1) prospective clinical studies in humans involving at least 10 patients and investigating VNS for the treatment of medically refractory epilepsy; (2) retrospective studies with > 50 patients with epilepsy syndromes for which there is little published evidence (e.g., LGS); and (3) meta-analyses.

Exclusion Criteria: Animal studies; preclinical studies; studies investigating technical aspects of VNS; and studies assessing primarily medication use in patients undergoing VNS.

Selected Reviews and Studies

One meta-analysis (Privitera et al., 2002), and 39 primary studies were selected for this detailed review, and the selected evidence is summarized in Table 1. The primary

studies consisted of data from two randomized trials, four nonrandomized controlled trials, and 33 uncontrolled studies. Several systematic reviews were identified but excluded from the detailed review since they did not provide additional evidence or did not meet the quality criteria.

The early published evidence consisted predominately of the Cyberonics #E01 to #E05 series of clinical studies.

- #E01 and #E02: Prospective, small, single-blind studies with patients serving as their own control (Penry & Dean, 1990; Uthman et al., 1990; Uthman et al., 1993).
- #E03 and #E05: Large randomized, blinded, controlled trials of high-stimulation versus low-stimulation VNS (Ben-Menachem et al., 1994; George et al., 1994; Handforth et al., 1998; Holder, Wernicke, & Tarver, 1992; Salinsky, Uthman, Ristanovic, Wernicke, & Tarver, 1996; Vagus Nerve Stimulation Study Group, 1995).
- #E04: Uncontrolled, open-label, compassionate-use trial (Labar et al., 1999).
- #XE5: Open extension trial of VNS study #E05 (Amar, DeGiorgio, Tarver, & Apuzzo, 1999; DeGiorgio et al., 2000; Labar, Murphy, & Tecoma, 1999).

Patients from these studies also serve as the cohort of the VNS patient outcomes registry that is maintained by Cyberonics Inc. The main difference between VNS studies #E03 and #E05 involved the exclusion criteria; #E05 excluded patients with simple rather than complex partial seizures and those with prior vagus nerve or antiepilepsy surgery. After completion of the #E05 trial, patients had the opportunity to enroll in an open-label, nonblinded, 12-month extension of this study (#XE5). These larger studies were performed by the First International Vagus Nerve Stimulation Study Group in collaboration with Cyberonics Inc. and involved a number of different centers and patient populations. Some studies used the patient registry and data from VNS studies #E01 to #E05 for retrospective analysis of specific patient subgroups (Morris & Mueller, 1999; Murphy, Hornig, & Schallert, 1995; Sirven et al., 2000). Additional evidence was derived from several prospective, randomized and nonrandomized, controlled or comparative studies (Ben-Menachem, Hellstrom, Waldton, & Augustinsson, 1999; McGlone et al., 2008; Nei, O'Connor, Liporace, & Sperling, 2006; Scherrmann, Hoppe, Kral, Schramm, & Elger, 2001; Sherman et al., 2008). The remaining evidence consisted of prospective uncontrolled studies, case series, and retrospective studies (Amar, Apuzzo, & Liu, 2004; Annegers, Coan, Hauser, & Leestma, 2000; Chavel, Westerveld, & Spencer, 2003; De Herdt et al., 2007; Helmers et al., 2001; Holmes, Silbergeld, Drouhard, Wilensky, & Ojemann, 2004; Hornig, Murphy, Schallert, & Tilton, 1997; Hosain et al., 2000; Huf, Mamelak, & Kneedy-Cayem, 2005; Labar, 2004; Lundgren, Amark, Blennow, Stromblad, & Wallstedt, 1998; Majoie et al., 2001; Mikati et al., 2009; Murphy et al., 1995; Parker et al., 1999; Rossignol et al., 2009; Rychlicki et al., 2006; Spanaki, Allen, Mueller, & Morris, 2004; Uthman et al., 2004; Vonck et al., 2004; You et al., 2007). The results of these studies are summarized and critiqued in

the following section. Please view the evidence table for quality ratings for specific studies.

Quality Assessment

Systematic Reviews: The quality of selected *systematic reviews* was evaluated with the MED Project checklist for systematic reviews (Appendix I).

Primary Studies: Individual primary studies were first rated based on study design:

- Good = randomized controlled trials (RCTs).
- Fair = quasi-RCT, nonrandomized controlled study, or nonrandomized comparative study).
- Poor = studies without concurrent control or comparison groups.

The quality ratings for studies were then modified based on study strengths and limitations, using the MED Project checklists for RCTs (Appendix II) and cohort studies (Appendix III). For uncontrolled/noncomparison studies, no formal checklist was used. However, quality factors were detailed in the evidence tables and could potentially upgrade an uncontrolled study to a higher quality rating.

Body of Evidence Evaluation: For each clinically significant outcome, e.g., healing or functional status, the overall quality of the body of evidence was evaluated according to the GRADE guidelines (Atkins et al., 2004; Guyatt et al., 2008). The following categories were observed:

- High = further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, or no estimate of effect can be made at this time.

In the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, evidence based on RCTs is considered the highest quality evidence. However, a high quality rating can be downgraded on the basis of the methodological limitations of individual studies and other factors such as inconsistency across studies. Evidence from study designs not usually considered of high quality, i.e., nonrandomized controlled or comparative studies and uncontrolled studies can sometimes be upgraded.

Other Considerations: When the quality of the evidence has been graded for each outcome, several additional considerations are important before recommendations can be made. These considerations include the relative importance of the various outcomes, the magnitude (clinical significance) of observed benefits, the benefits of the technology

weighed against observed and potential harms, the availability and effectiveness of alternatives, and patient compliance issues. Such issues are reviewed in the overall conclusion of this rapid review.

FINDINGS

The body of evidence reviewed involved studies with 13 to 454 patients, as well as registry data for 4743 patients with medically refractory epilepsy syndromes and one retrospective analysis involving 1819 patients of the incidence of sudden death in epilepsy (SUDEP). Most patients had partial seizures with or without secondary generalized seizures; less evidence was available for patients with generalized seizures, Lennox-Gastaut seizures, or other epileptic syndromes. In the studies evaluating VNS in patients with medically intractable epilepsy, the term "medically intractable" was generally used for patients who experienced at least six seizures per month while taking antiepileptic medications. Several studies also involved individuals with surgically intractable seizures; these patients did not have epileptogenic foci amenable to resection or had undergone unsuccessful surgical procedures to control their epilepsy. These studies performed VNS using the NeuroCybernetic Prosthesis (NCP) System (Cyberonics Inc.), also referred to as the VNS Therapy System. Device implantation was performed under general or local anesthesia, and the programmable generator was implanted subcutaneously in the chest where it delivered pulses of current via electrodes attached to the vagus nerve in the left side of the neck. VNS was activated following a two-week recovery period following surgery. In the subsequent two weeks, the stimulation parameters were adjusted for each patient individually to the maximum level comfortable to the patient. The studies evaluated VNS for up to 10 years. Change in seizure frequency was the most commonly used outcome measure. Complications and QOL were also assessed, and seizure duration and intensity played a lesser role. The studies described reduction in seizure frequency either as mean (the average reduction in numbers of seizures) or median (the middle of a range of values). Patients who experienced greater than 50% seizure reduction were often referred to as responders.

There are several ways in which reduction in seizure frequency in a given time frame can be evaluated: an absolute reduction in the number of seizures; a percentage reduction in seizure frequency; and the proportion of patients achieving a threshold of seizure reduction (e.g., ≥ 50%, ≥ 75%). The latter method measures how many patients experience a clinically meaningful improvement in seizure frequency. Measuring absolute or relative change from baseline compared with sham treatment is by itself not necessarily meaningful because a statistical difference does not necessarily equate to a treatment effect that can be felt by the patient. One RCT had sufficient statistical power to detect a 15% difference in seizure frequency between active and sham VNS. One can argue that a 15% reduction may not be meaningful to the patient. However, in consideration that each epileptic seizure poses a significant health risk to the patient, including death, 15% is an acceptable threshold. However, it does not mean that a statistical difference between active and sham VNS equals a large treatment benefit.

Therefore, it is important to report not only the statistically significant reduction in seizure frequency from baseline but also the percentage of patients achieving a moderate to large treatment benefit (e.g., ≥ 50%, ≥ 75% reduction in seizure frequency).

1. Is the use of vagus nerve stimulators plus antiepileptic medication effective, compared with medication alone, in reducing the frequency or severity of clinical seizures or in improving quality of life?

Effect of VNS on seizure frequency

VNS for partial seizures

The Cochrane Collaboration published a meta-analysis evaluating VNS for partial seizures (Privitera et al., 2002). The review included randomized double-blind controlled trials of VNS in children and adults with drug-resistant partial seizures. Based on this analysis, the overall 95% odds ratio for a 50% reduction of seizure frequency when receiving high-stimulation versus low stimulation was 1.93 (confidence intervals [CI], 1.11 to 3.35); odds ratios were 1.84 and 1.99 for the worst-case and best-case scenario, respectively.

Two RCTs evaluated the effect of VNS on seizure frequency: the #E03 (Holder et al., 1992; Ben-Manachem et al., 1994; Vagus Nerve Stimulation Group, 1995) and #E05 (Handforth et al., 1998) multicenter, randomized, double-blind trials. Both studies provided high-quality randomized evidence with appropriate scheme and double-blinded. Furthermore, the studies used sufficiently large sample sizes to detect at least a 15% difference in seizure frequency and used low stimulation as a placebo control. The latter is especially important because VNS stimulation can be felt, and low stimulation VNS preserves blinding. A weakness of these studies is that the 14-week treatment time was relatively short.

In both studies, active VNS significantly reduced overall seizure rates from baseline compared with sham VNS. In the #E03 study, active VNS significantly reduced total seizure frequency by 24.5% from baseline compared with 6.1% in the sham VNS group (P=0.01). In the #E05 study, active VNS significantly reduced total seizure frequency from baseline by 27.9% versus 15.2% with sham VNS (P=0.04) overall and by 26.6% and 13.4%, respectively, for partial seizures. In the #E03 study, the proportion of patients experiencing ≥ 50% improvement in seizure frequency was significantly larger in the active treatment group (31%) compared with the sham treatment group (13%) (P=0.02). In the #E05 study, the proportion of patients experiencing ≥ 50% reduction of seizure frequency was not significantly different for active VNS (23.4%) and sham VNS (15.7); however, more patients had ≥75% reduction in seizure frequency for active VNS (10.6%) than patients in the sham VNS group (2.0%) (P=0.015). The placebo effect in the #E03 was relatively small, while in the #E05 group, the extent of the placebo effect was similar to those observed in other clinical trials for chronic, severe MDD or bipolar disorders.

Some patients derived benefit from low-level VNS, a treatment that was originally intended as a placebo control. Low-stimulation parameters were designed to provoke a strong enough stimulus to be sensed by the patient but were thought to be below the threshold required for VNS. It is, therefore, likely that the placebo effect may have contributed to the observed improvement in patient status during low-stimulus VNS, although a true treatment effect of low-level stimulation cannot be entirely excluded. However, this strengthens rather than weakens the studies because it suggests that the actual treatment benefit may be higher.

A small, prospective nonrandomized study using age-matched and sex-matched control groups compared the efficacy of VNS (n=16) with medical treatment (n=9) and epilepsy surgery (n=10). At 12 months, 18.8% of patients in the VNS group achieved ≥ 50%. The objective of the study was to evaluate and compare QOL (see following sections) and did not report on seizure frequencies in the control groups (McGlone et al., 2008).

The evidence from uncontrolled studies support the evidence from higher-level studies concluding that VNS can reduce seizure frequency, with approximately 20% to 75% of patients experiencing at least a 50% mean reduction; less than 10% were seizure free. Long-term follow-up studies have demonstrated that the benefits obtained with VNS can be sustained for two to up to 10 years, and it appears that responding patients experienced further reductions in seizure frequency over time (Amar et al., 1999; DeGiorgio et al., 2000; Kabir et al., 2009; Kuba et al., 2009; Morris & Mueller, 1999; Murphy, 1999; Rychlicki et al., 2006; Spanaki, Allen, Mueller, & Morris, 2004; Uthman et al., 2004).

Vagus Nerve Stimulation for generalized seizures and Lennox-Gastaut Syndrome

One nonrandomized controlled trial compared VNS (n=25) with callosotomy (n=53) for the treatment of generalized seizures (Nei et al., 2006). There were no statistically significant differences between the two groups in the proportion of patients achieving ≥ 50% or ≥ 80% reduction in seizure frequency. This result fails to show superiority of one technique over the other. However, the sample size was not large enough to demonstrate equivalence. Furthermore, patients receiving VNS had significantly longer duration of epilepsy prior to the study than patients undergoing callosotomy, which confounds the study results. Another confounder is the length of clinical follow-up, which was significantly longer for callosotomy (mean, 4.5 years) versus VNS (mean, 1.3 years). Therefore, the limitations of this study do not permit definitive conclusions.

Additional evidence from uncontrolled studies of VNS in the treatment of generalized epilepsy (Ben-Menachem et al., 1999; Chavel et al., 2003; De Herdt et al., 2007; Holmes et al., 2004; Labar et al., 1999; Mikati et al., 2009; Vonck et al., 2004; You et al., 2007) and Lennox-Gastaut syndrome (LGS) (Ben-Menachem et al., 1999; Chavel et al., 2003; Frost et al., 2001; Helmers et al., 2001; Hornig et al., 1997; Hosain et al., 2000; Majoie, Berfelo, Aldenkamp, Renier, & Kessels, 2005; Murphy et al., 1995; Rossignol et al., 2009) suggests that VNS therapy may also be effective for these types of seizures; the quality of the evidence was poor, and the studies were not sufficiently powered to

estimate the treatment benefit and to draw conclusions regarding seizure type and responsiveness to VNS. The results of these initial studies will need to be confirmed in randomized controlled trials before definitive conclusions can be drawn.

Effect of VNS on Quality of Life (QOL)

A number of studies evaluated the effect of VNS on QOL in patients with epileptic syndromes (Amar et al., 1999; Chavel et al., 2003; DeGiorgio et al., 2000; Helmers et al., 2001; Huf et al., 2005; Lundgren et al., 1998; Frost et al., 2001; Majoie et al., 2001; Majoie et al., 2005; McGlone et al., 2008; Mikati et al., 2009; Murphy, 1999; Parker et al., 1999; Rychlicki et al., 2006; Sherman et al., 2008; Sirven et al., 2000; You et al., 2007). Several different instruments assessed QOL, including the Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Child Epilepsy Questionnaire Parental Form (CEQ-P [II]), Client Development Evaluation Report instrument (CDER), Epilepsy Surgery Inventory-55 (ESI-55), Global rating of quality of life scale, Hague Seizure Severity Scale (HASS), Hague Side Effects Scale (HASES), Impact of Childhood Neurologic Disability Scale-30 (ICND-30), Memory Observation Questionnaire (MOQ), Quality of Life in Epilepsy Instrument-89 (QOLIE-89), Korean version of the Quality of Life in Childhood Epilepsy questionnaire (K-QOLCE), Quality-of-Life in Childhood Epilepsy Questionnaire (QOLCE), Vineland adaptive behavior scale (VBAS), Wechsler Memory Scale-III (WMS-III).

The studies evaluated different parameters that were not always comparable across studies. However, the studies used standardized instruments with established reliability and validity.

Evidence for partial seizures

The VNS study #E03 evaluated QOL, enrolling 114 pts who were assigned to high- or low-stimulation VNS (Holder et al., 1992; Ben-Menachem et al., 1994). However, QOL was not evaluated in the complete patient population but only on a subset of patients for whom data were available at this time because enrollment was still in progress. The study did not use a standardized questionnaire to evaluate QOL but used a 100-mm analog scale. Improvements in QOL were indicated to the right of a center line (maximum +50 mm), while deterioration in QOL was indicated to the left of the center line (maximum –50 mm). Because of study design limitations, the quality of this study was downgraded from good to fair. Patients, caregivers, and investigators measured QOL on this scale, but only the investigator scale showed a clinically significant difference between the active and sham VNS groups, with active VNS showing greater improvement in QOL. The exact data were not reported in the text. The investigators were blinded to the treatment allocation, suggesting that investigator bias is not likely. Nevertheless, the analog scale does not permit interpretation as to what areas of the patient's life were affected. In addition, the treatment period was only 14 weeks, and it is not certain whether these improvements can be maintained long term.

There was evidence from two prospective nonrandomized controlled trials evaluating the effect of VNS on QOL in patients with medically refractory epilepsy (McGlone et al., 2008; Sherman et al., 2008). In addition, one large retrospective registry study compared patients undergoing VNS who had previously undergone cranial surgery with those that had not (Amar et al., 2004).

This retrospective review of a patient registry containing data from 4743 patients, of which 921 had undergone cranial epilepsy surgery prior to VNS, and 3822 patients who had not undergone cranial epilepsy surgery prior to receiving VNS (Amar et al., 2004). Physician assessment of QOL was used to measure changes in alertness, verbal communication, memory, school/professional achievement, mood, postictal state, and seizure clustering versus baseline. For each parameter of QOL, one of five responses was selected: much better, better, no change, worse, or much worse. At 3 months treatment with VNS, there was statistically significant improvement in QOL for patients who had not undergone surgery prior to VNS for all elements of the QOL instrument. These differences were lost by 24 months with the exception of alertness, for which a statistically significant difference was still present at this time point. The use of only one instrument to evaluate QOL, differences in sample size for the different time points when QOL was evaluated, and a smaller sample size for the surgery group limit the quality of this study for assessing changes in QOL.

A recent prospective nonrandomized controlled study evaluated changes in QOL in patients receiving VNS (16 patients), medical treatment (9 patients), or had undergone antiepileptic surgery (10 patients) (McGlone et al., 2008). The study found improvements in QOL (assessed with QOLIE-89 and MOQ-SA) from baseline for all three groups but there were no differences among the three treatments. However, the study was not sufficiently powered to detect small to moderate differences.

Sherman et al. (2008) conducted a prospective nonrandomized controlled study involving 53 patients. Baseline QOL was better in the control versus the VNS group, confounding the interpretation of the results. QOL remained unchanged in most patients, and there was no difference between the control and the treatment group. QOL increased by 33% (ICNDS instrument) and 14% (Global QOL instrument) for patients in the VNS group; the respective values for the control group were 11% and 6%. QOL did not improve more in patients who responded to VNS with at least a 50% reduction in seizure frequency compared with nonresponders. However, the sample size for this subgroup analysis may have been too small to detect a small to moderate treatment effect.

Several uncontrolled studies evaluated the effect of VNS on QOL in patients with medically refractory epilepsy (Amar et al., 1999; Chavel et al., 2003; DeGiorgio et al., 2000; Helmers et al., 2001; Huf et al., 2005; Lundgren et al., 1998; Mikati et al., 2009; Parker et al., 1999; Rychlicki et al., 2006; Sirven et al., 2000). The studies used different instruments to assess QOL and the results are, therefore, not comparable across studies.

VNS improved elements of QOL in some patients, but specific improvements were inconsistent among studies. While VNS improved QOL in several studies (Amar et al., 1999; Helmers et al., 2001; Huf et al., 2005; Lundgren et al., 1998; Rossignol et al., 2009; Rychlicki et al., 2006; Sirven et al., 2000), in others, especially in studies with very small sample sizes, improvements were not significant or were noted in only one or two domains (Chavel et al., 2003; Mikati et al., 2009; Parker et al., 1999).

Evidence for generalized seizures and Lennox-Gastaut Syndrome

Evidence was available from uncontrolled studies for patients with generalized seizures (You et al., 2007) and LGS (Frost et al., 2001; Majoie et al., 2001; Majoie et al., 2005). QOL improved for generalized seizures for all measured parameters of the Korean version of the QOL in children with epilepsy questionnaire. With the exception of mood, VNS did not improve QOL in two studies of VNS LGS (Majoie et al., 2001; Majoie et al., 2005), while the third study reported improvements in QOL for up to 6 months (Frost et al., 2001).

Summary of Evidence for Key Question #1

There is evidence that VNS can reduce seizure frequency, with 21% to 75% of patients experiencing at least a 50% mean reduction. The treatment benefit is maintained for up to 10 years. Adults and children older than age 12 years seem to benefit equally from the treatment. Most studies to date have included patients with a broad range of epilepsy syndromes associated with intractable partial seizures classified as simple, complex, or secondarily generalized. Limited evidence was available for generalized seizures, LGS, and other epileptic syndromes. While the results from these studies suggest that VNS therapy may also be effective for these types of seizures, the quality of the evidence was poor, and none of the studies was sufficiently powered to estimate the treatment benefit and to draw conclusions regarding seizure type and responsiveness to VNS. The results of these initial studies will need to be confirmed in randomized controlled trials before any definitive conclusions can be drawn.

A number of studies evaluated the effect of VNS on QOL in patients with epileptic syndromes. The results showed that VNS may improve elements of QOL in some patients, but specific number and type of improvements were inconsistent among studies. While VNS improved QOL in several studies, in others, especially in studies with very small sample size, improvements were not significant or were noted in only one or two domains; however, insufficient power to detect a significant effect makes interpretation of these results difficult.

Results from a number of uncontrolled studies suggest that VNS therapy may also be effective for generalized epilepsy and LGS. The quality of the evidence was poor, and the studies were not sufficiently powered to estimate the treatment benefit and to draw conclusions regarding seizure type and responsiveness to VNS. The results of these initial studies will need to be confirmed in randomized controlled trials before definitive conclusions can be drawn.

2. Are vagus nerve stimulators safe?

VNS for partial seizures

The Cochrane Collaboration published a meta-analysis evaluating VNS for partial seizures (Privitera et al., 2002). The review included randomized double-blind controlled trials of VNS in children and adults with drug-resistant partial seizures. The odds ratios for adverse effects related to high-stimulation VNS were 4.5 for hoarseness and 2.65 for dyspnea; for adverse effects related to device implantation, the odds ratios were 4.74 for hoarseness, 2.97 for cough, and 6.36 for paresthesia. There was no statistically significant trend for pain. Finally, for adverse effects likely attributable to implantation plus electrical stimulation, the odds ratios were 14.52 for hoarseness, 3.12 for cough, 5.40 for dyspnea, 3.83 for pain, and 8.21 for paresthesia.

Limited data on the safety of VNS were available from the two randomized controlled trials involving 114 patients (#E03) and 198 patients (#E05) (Ben-Menachem et al., 1994; George et al., 1994; Handforth et al., 1998; Holder, Wernicke, & Tarver, 1992; Salinsky, Uthman, Ristanovic, Wernicke, & Tarver, 1996; Vagus Nerve Stimulation Study Group, 1995). For both studies, the controlled treatment phase did not exceed 14 weeks. The studies only reported complications occurring in > 5% (#E03) or > 10% (#E05) of patients. Overall, with few exceptions, complication rates were similar for sham VNS and active VNS in both studies. In the #E03 trial (Ben-Menachem et al., 1994; George et al., 1994; Holder, Wernicke, & Tarver, 1992; Salinsky, Uthman, Ristanovic, Wernicke, & Tarver, 1996; Vagus Nerve Stimulation Study Group, 1995), hoarseness/voice changes occurred in significantly more patients receiving the active treatment (37.3%) compared with sham VNS (13.3%). In the #E05 study (Handforth et al., 1998), statistically significant higher rates were observed for voice alterations (66.3%) and dyspnea (25.3%) in the active group versus the sham VNS group (30.1% and 10.7%, respectively). These studies did not include a control group that received treatment as usual and patients in the sham VNS group also received stimulation, although at a much lower frequency. It is, therefore, possible that some or all complications are related to VNS but that only voice alterations and dyspnea were more pronounced with higher stimulation settings.

Safety data from uncontrolled studies were available for a time frame of up to 10 years (Amar et al., 1999; Ben-Menachem et al., 1999; DeGiorgio et al., 2000; George et al., 1994; Helmers et al., 2001; Hornig et al., 1997; Huf et al., 2005; Kabir et al., 2009; Kuba et al., 2009; Lundgren et al., 1998; Morris & Mueller, 1999; Murphy, 1999; Murphy et al., 1995; Parker et al., 1999; Penry & Dean, 1990; Rossignol et al., 2009; Rychlicki et al., 2006; Salinsky et al., 2001; Sirven et al., 2000; Vonck et al., 2004). Side effects were generally mild, occurred only during stimulation, and decreased over time or could be resolved by changing device parameters. Complications possibly related to VNS included: voice alteration during stimulation; hoarseness; cough; neck, ear, throat, chest, arm, and incisional pain; headache; dizziness; insomnia; increased drooling; paresthesia; dyspnea; dysphagia; fatigue; fever; nausea; vomiting; pneumonia; shortness of breath; pharyngitis; depression; aspiration; muscle spasms; hiccups;

wound infection; anorexia; lead breakage and device failure. While adjusting the stimulation parameters reversed some complications such as voice alterations, other complications (e.g., dyspnea, pain) required treatment or were permanent. In some cases, the device had to be repositioned or removed, although successful reimplantation was often possible. Pediatric patients experienced side effects similar to those experienced by adults and, as in adults, these improved over time (Hosain et al., 2000; Kirse et al., 2002).

Evidence from one cohort study involving 1819 patients indicates that VNS may not increase mortality rates from sudden unexplained death in epilepsy (SUDEP) (Annegers et al., 2000). The calculated overall death rates in this study were 4.1 per 1000 for patients using VNS versus 4.5 per 1000 for a normal medically refractory epilepsy population. Furthermore, death rates declined from 5.5 per 1000 during the first 2 years of the study to 1.7 per 1000 for subsequent years.

VNS for generalized epilepsy and Lennox-Gastaut Syndrome

One prospective study compared complications in 53 patients who underwent corpus callosotomy with 25 patients with generalized epilepsy who received VNS (Nei et al., 2006). The mean follow-up was 4.5 years for corpus callosotomy and 1.3 years for VNS. Overall complication rates were higher for the corpus callosotomy group (21%) than the VNS group (8%). Furthermore, complication rates were 3.8% in the corpus callosotomy group, while none were permanent in the VNS group. Serious complications associated with corpus callosotomy included: death (1), status epilepticus (1), gait difficulty (2), osteomyelitis (1), hemiparesis (2), disconnection syndrome (2), and deep venous thrombosis (1). In the VNS group, one device had a defective battery, and infection at the surgical site occurred in one patient; however, the study was of poor quality because the sample size was lower for the VNS group, follow-up times varied between the two groups, and VNS patients had a longer duration of epilepsy prior to VNS than the surgical group. Therefore, the results must be interpreted with caution.

Additional evidence from uncontrolled trials of VNS in the treatment of generalized epilepsy (Ben-Menachem et al., 1999; Holmes et al., 2004; Labar et al., 1999; Vonck et al., 2004; You et al., 2007) and LGS (Ben-Menachem et al., 1999; Frost et al., 2001; Helmers et al., 2001; Hornig et al., 1997; Hosain et al., 2000; Majoie et al., 2005; Murphy et al., 1995; Rossignol et al., 2009) suggests that these patients may experience complications similar to patients with partial epilepsy and are not at a higher risk for complications. However, evidence from controlled studies is needed to confirm these results.

Summary of Evidence for Key Question #2:

Safety data for VNS are available for a time frame of up to 10 years. The most common complications associated with VNS therapy were voice alterations, hoarseness, cough, pain, dyspnea, infection, paresthesia, headache, and pharyngitis. These problems were generally mild, occurred only during stimulation, and decreased over time or could be resolved by changing device parameters. In some cases, the NCP had to be repositioned or removed, due to infection or device malfunction, but in most cases, the device was successfully exchanged or reimplanted. Studies that compared the incidence of definite/probable SUDEP with the expected baseline rate for epilepsy revealed no increased risk of mortality that could be attributed to the use of VNS devices. Preliminary evidence suggests that patients

with generalized seizures and LGS may experience similar complications and are not at a higher risk for negative side effects than patients with partial seizures.

3. Does effectiveness vary by age group, response to antiepileptics, or other patient characteristics?

Very few studies investigated efficacy and safety of VNS in patient subgroups. The current evidence supports the use of VNS for severe, treatment-resistant epilepsy in patients older than 12 years of age. There is presently no indication that effectiveness and safety vary with patient characteristics. Currently, studies have evaluated the use of VNS in children12 years of age or younger (this is the lowest age limit for which VNS is FDA approved) (Hornig et al., 1997; Murphy, 1999; Rossignol et al., 2009), adults 50 years of age or older (Sirven et al., 2000); patients who had undergone prior surgery (Amar et al., 2004), and patients with an intelligence quotient (IQ) lower than 70 (Huf et al., 2005).

The use of VNS in patients who had previous cranial surgery has been addressed through analysis of the Cyberonics VNS therapy patient outcome registry (Amar et al., 2004). Seizure frequency for the 981 individuals who had VNS implantation after cranial surgery was compared with that seen in patients who had no prior surgery. The result of this analysis suggests that VNS therapy is more effective for patients who had no previous surgical treatment for epilepsy.

While young children were included in most clinical trials, these studies did not always report the results for young children separately from those for adults. A pediatric pilot study demonstrated efficacy in children younger than 12 years of age. Hornig et al. (1997) noted that there are significant advantages for the use of VNS treatment in children compared with medical management alone—no adverse cognitive effects, no drug interactions, and no issues of patient compliance—as therapy is involuntary and automatic. Murphy (1999), in a study enrolling 60 children, noted that the treatment benefits for children younger than 12 years of age were similar to older children. In a recent study, Rossignol et al. (2009) evaluated VNS in 28 children, aged 2 months to 7 years, with various epileptic syndromes. At 2 years, mean seizure reduction was 53% per patient, and 67% to 100% of patients responded with > 50% decrease in seizure frequency. For 26 of 28 patients, caregivers noted that VNS improved sleep. In 69% of children, VNS improved alertness, playfulness, and global interaction. Overall, these results suggest that VNS is effective in improving seizure frequency and QOL in very young children. However, additional data are required to confirm these findings.

In another study (Sirven et al., 2000), VNS therapy was equally effective and improved over time in adults older than 50 years of age, and the side effects were mild and transient. Drug interactions were not apparent during the course of this study. In the authors' opinion, VNS may, therefore, offer an advantage for older patients who often take medications in addition to antiepileptic drugs.

Huf et al. (2005) evaluated the use of VNS in patients with an IQ of less than 70. The study enrolled 40 patients with medically refractory epilepsy and lasted for 2 years. Overall, 28% of patients experienced 50% or greater reduction in seizure frequency. VNS also improved QOL, assessed with the CDER instrument, and reduced the number of epilepsy-related hospitalizations from 40 in the year prior to VNS to 9 in the first and 18 in the second year following implantation.

Predictors of a treatment response have not been established. Labar et al. (1999) observed that patients with higher baseline seizure frequency and those who were older at epilepsy onset were more responsive to VNS therapy, but further research will be necessary to substantiate this finding. The patients in this study had generalized epilepsy.

Summary of Evidence for Key Question #3

There is currently insufficient evidence to suggest that effectiveness may vary by patient characteristics. However, the current evidence from small pilot studies suggests that VNS may also be effective in patients 12 years of age or younger and those older than 50 years of age. Furthermore, VNS may be more effective for patients who had no previous surgical treatment for epilepsy. Predictors of a treatment response have not been established. Labar et al. (1999) observed that patients with higher baseline seizure frequency and those who were older at epilepsy onset were more responsive to VNS therapy. Additional research is required to substantiate these findings.

Strengths and Limitations of the Evidence

A high level of evidence exists for the investigation of VNS on seizure frequency. The strongest evidence is composed of two randomized placebo-controlled trials (Vagus Nerve Stimulation Study #E03, #E05) (Ben-Menachem et al., 1994; George et al., 1994; Handforth et al., 1998; Holder, Wernicke, & Tarver, 1992; Salinsky, Uthman, Ristanovic, Wernicke, & Tarver, 1996; Vagus Nerve Stimulation Study Group, 1995); one uncontrolled, open-label, compassionate use trial (#E04) (Labar et al., 1999); and an open-extension trial of VNS study #E05 (#XE5) (Amar, DeGiorgio, Tarver, & Apuzzo, 1999; DeGiorgio et al., 2000; Labar, Murphy, & Tecoma, 1999). A strong feature of the study design in the randomized controlled studies is that they used a low-stimulation setting as a placebo control. The patient senses stimulation, and, by providing low stimulation, the patients are less likely to be able to discern true stimulation from placebo. In addition, sample sizes were large enough to detect a 15% difference in seizure frequency. Considering the gravity of these patient's health conditions, this is a clinically significant treatment effect. The First International Vagus Nerve Stimulation Study Group conducted these studies in collaboration with Cyberonics Inc., the manufacturer of the neurocybernetic device.

There is a moderate level of evidence regarding the effect of VNS on QOL. The studies used a large number of instruments measuring different parameters of QOL. The results were inconsistent across studies; however, most inconsistencies may have been due to

studies that did not have sufficient statistical power to detect an effect of VNS on QOL. The results from these studies must, therefore, be interpreted with caution, and further investigation using a randomized controlled study design will be necessary to confirm these observations.

There is a high level of evidence for short-term safety and a moderate level of evidence for long-term safety of VNS for partial epilepsy. The long-term evidence was limited by the lack of a control group and randomization.

A low level of evidence was available for determining whether outcomes are different depending on sex and age and other patient characteristics.

There is a low level of evidence for patients with generalized epilepsy and LGS. While a few small nonrandomized controlled and comparative studies were available, evidence for efficacy of VNS therapy for generalized epilepsy and LGS still stems mostly from lower-level evidence, including retrospective analyses, chart analyses, or small prospective, open-label trials lacking appropriate control groups. Small sample size, lack of control groups, and lack of blinded assessment were some of the criteria compromising the quality of these studies. Furthermore, in some studies, medical treatment was adjusted in the VNS group, thus possibly confounding the results.

Table 1. Summary of Primary Studies Evaluating the Efficacy and Safety of Vagus Nerve Stimulation

Key: AED(s), antiepileptic drug(s); BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CDER, Client Development Evaluation Report instrument; CEQ-P, Child Epilepsy Questionnaire Parental Form; CPS, complex partial seizures; dx, diagnosis; dx'd, diagnosed; EEG, electroencephalogram; ESI-55, Epilepsy Surgery Inventory-55; f/u, follow-up; grp(s), group(s); GTC, generalized tonic-clonic (seizures); HASES, Hague Side Effects Scale; HASS, Hague Seizure Severity Scale; hx, history; Hz, hertz; ICND-30, Impact of Childhood Neurologic Disability Scale-30; IQ, intelligence quotient; ITT, intention-to-treat; K-QOLCE, Korean version of the Quality of Life in Childhood Epilepsy questionnaire; LGS, Lennox-Gastaut syndrome; mA, milliampere; MOQ, Memory Observation Questionnaire; MRI, magnetic resonance imaging; μsec, milliseconds; NA, not applicable; NCP, NeuroCybernetic Prosthesis (Cyberonics Inc.); NR, not reported; NS, not statistically significant; PDD, pervasive developmental disorder; PGS, primary generalized seizures; postop, postoperative(ly); preop, preoperative(ly); PS, partial seizures; pt(s), patient(s); QOL, quality of life; QOLCE, Quality-of-Life in Childhood Epilepsy Questionnaire; QOLIN-89, Quality of Life in Epilepsy Instrument-89; SD, standard deviation; stim, stimulation; SPS, simple partial seizures; SUDEP, sudden unexplained death in epilepsy; tx, treatment (or therapy); tx'd, treated; VNS, vagus nerve stimulation; WAI, Working Alliance Inventory scale; WISC, Wechsler Intelligence Scale; WMS-III, Wechsler Memory Scale-III

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
Randomized controlled trials				
Holder et al. (1992); Ben-Menachem et al. (1994); Vagus Nerve Stimulation Study Group (1995) First International Vagus Nerve Stimulation Study Group, 17 centers in Canada, Germany, the Netherlands, Sweden, and U.S. VNS Study #E03; multicenter, prospective, randomized, blinded parallel study to compare short-term and long-term effects of high-level (presumed therapeutic) and low-level (presumed ineffective) VNS *F/u:* 14 wks; last 12 wks used for efficacy analysis *Time frame:* NR	n=114 pts (age 14-57 yrs) randomized to: High-stim grp: n=54 (mean age 33 yrs; 61% male, 39% female; mean seizures/day 1.49; duration of epilepsy, 23.1 yrs; mean # AEDs, 2) Low-stim grp: n=60 (mean age 33.5 yrs; 63% male, 37% female; mean seizures/day 0.82; duration of epilepsy, 20 yrs; mean # AEDs) *Inclusion criteria:* Out- or inpts; age 12-60 yrs; ≥6 seizures/mo over 3 mos; seizures not adequately controlled w/ AEDs at stable concentrations; simple or complex PS (secondary generalized seizures permitted); ability to understand and give consent; use of accepted birth control in women; pts who have received investigational AEDs permitted if 5x	12 wks baseline seizure hx before implantation w/ NCP. High-stim: 20-50 Hz, 500 μsec; 30-90 secs stim on, 30 secs stim off; × 14 wks followed by indefinite open-extension phase Low-stim: 1-2 Hz, 130 μsec; 5-10 secs stim on, 60-180 secs stim off; × 14 wks followed by indefinite open-extension phase *Outcome measures:* Primary: % difference in overall seizure frequency during final 12 wks of tx vs baseline Secondary: Absolute difference in seizure frequency; % pts achieving ≥50% seizure reduction; QOL (pt, caretaker, investigator) in first report involving pts (global	Only pts in the high-stim grp had significant reduction in seizure frequency vs baseline. During final 12 wks of VNS tx, mean reduction in seizure frequency vs baseline values was 24.5% for high-stim, 6.1% for low-stim (*P*=0.01). 31% pts in high-stim grp had seizure frequency reduction ≥50% vs 13% of pts in low-stim grp (*P*=0.02). High-stim pts who experienced auras had more reduction in seizure frequency than those not reporting auras (52% reduction vs 10%, respectively). Both grps showed improved QOL, but high-stim grp showed greater improvement. The only statistically significant difference was for investigator rating (exact data NR). *Complications* occurring in >5% of pts (% pts high-stim grp, % pts low-stim grp)*:* Hoarseness/voice changes (37.2%, 13.3%), throat pain (11.1%, 11.7%), coughing (7.4%, 8.3%), dyspnea (5.6%, 1.7%), paresthesia (5.6%, 3.3%), muscle pain (5.6%, 1.7%),	Results demonstrate that high-stim VNS can reduce seizure frequency in some pts w/ intractable seizures. NOTE: ITT analysis *Limitations:* Short tx time; different underlying pathophysiology of seizures in pts who experience auras, which may account for more favorable response in these pts; values for QOL were provided as graph, exact values and statistical analysis NR; QOL data not available for complete grp; no standardized instruments used to assess QOL *Quality:* Good (for assessing effect on seizure frequency); poor (for assessing QOL)

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Funding source: Cyberonics Inc.	mean elimination half-life + 2 wks have passed prior to study *Exclusion criteria:* Progressive neurological disease; prior cervical neurotomy; pregnancy; taking >3 AEDs; medical condition likely to deteriorate or result in hospitalization w/in 1 yr	rating using linear 100-mm analog scale, improvements and deteriorations were measured as deflections from the center line)	headache (1.8%, 8.3%); hoarseness/voice changes were significantly higher w/ high-stim than low-stim VNS.	
Handforth et al. (1998) West Los Angeles Veterans Administration Medical Center, Los Angeles, CA; First International Vagus Nerve Stimulation Study Group centers VNS Study #E05; multicenter, randomized, parallel, double-blind, prospective study to compare high-level w/ low-level VNS *F/u:* 3 mos *Time frame:* January 31, 1995 – August 29, 1996 *Funding source:* Cyberonics Inc.	n=198 pts were randomized but 2 were excluded from efficacy but not from safety analysis; 196 pts (range 13-60 yrs) randomized to: High-stim grp: n=94 Low-stim grp: n=102 *Inclusion criteria:* ≥6 medically refractory PS (complex partial or secondarily generalized convulsions) over 30 days, w/ ≤21 days between seizures; age 12–65 yrs; on 1–3 AEDs, stable for ≥1mo prior to study *Exclusion criteria:* Prior cervical vagotomy, VNS, brain stim, or resective epilepsy surgery; deteriorating neurologic or medical condition; pregnancy; cardiac or pulmonary disease; active peptic ulcer; hx of nonepileptic seizures	After 3-mo baseline period, pts implanted w/ NCP. Device was activated 2 wks after implantation. High-stim: VNS 30 Hz, 500 μsec × 3 mos Low-stim: 1 Hz, 130 μsec × 3 mos *Outcome measures:* Primary: Change in total seizure frequency Secondary: Global evaluation of pt status; proportion of pts experiencing ≥50% and ≥75% reduction in seizure frequency; changes in seizure frequency in seizures w/ altered awareness; complications	194 pts completed the study; 2 pts w/drew due to adverse events or lack of compliance. Outcomes for low-stim, high-stim grp: Mean %change in total seizure frequency from baseline: –15.2%, –27.9% (*P*=0.04) Change in PS (%): –13.4%, 26.6% (*P*=0.03) Reduction in seizure frequency (%pts): ≥50%: 15.7%, 23.4% ≥75%: 2.0%, 10.6% (*P*=0.015) High-stim grp had greater improvement in global evaluation scores, more voice alteration, and dyspnea, but no changes in physiologic indicators of gastric, cardiac, or pulmonary functions. *Complications occurring in >10% of pts (%pts; low-stim, high-stim):* Voice alterations (30.1%, 66.3%), cough (42.7%, 45.3%), pharyngitis (25.3%, 34.7%), pain (30.1%, 28.4%), dyspnea (10.7%, 25.3%), headache (23.3%, 24.2%), dyspepsia (12.6%, 17.9%), vomiting (13.6%, 17.9%), paresthesia (25.2%, 17.9%), nausea (20.4%, 14.7%), accidental injury (12.6%, 12.6%), fever (18.4%, 11.6%), infection (11.7%, 11.6%); statistically different were rates for voice alteration and dyspnea.	Results suggest that VNS was effective in controlling seizures and improving pt status. Presence of reported aura was not a predictor of VNS efficacy. Low dropout rate suggests that VNS is highly tolerable and accepted by pts. NOTE: Study had sufficient power to detect mean 15% difference between grps in the primary outcome. *Limitations:* Short tx time *Quality:* Good
Nonrandomized Controlled Trials				
Amar et al. (2004) Yale University School of Medicine, New Haven, Connecticut; University of California, Los Angeles, CA	n=4743 pts CS grp: n=921 pts who had previously undergone CS for epilepsy (median age 28 yrs, range	CS grp: Data were available for 591 pts at 3 mos, 373 at 6 mos, 368 at 12 mos, 224 at 18 mos, and 156 at 24 mos.	Median reduction in seizure frequency was statistically significantly greater in non-CS grp vs CS grp at 3, 6, 12, and 24 mos. Reduction in seizure frequency for CS and	Authors suggest that pts w/o prior surgery may benefit more from VNS. However, overall responder rates were similar between the 2 grps,

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Registry data for retrospective comparison of VNS tx and epilepsy surgery vs VNS tx and no surgery *F/u:* 24 mos *Time frame:* NR *Funding source:* NR; manufacturer involved in manuscript preparation; Cyberonics maintains the registry	1-66; 55.3% male, 44.7% female) Non-CS grp: n=3822 pts (51.5% male, 48.5% female) *Inclusion criteria:* Pts undergoing VNS for epilepsy *Exclusion criteria:* Pts undergoing intracraneal surgery for reasons other than epilepsy were not included in CS grp *Clinical hx (CS grp, non-CS grp) (%pts):* Localized seizures (75.2%, 57.0%), generalized seizures (22.1%, 39.5%), others (2.7%, 3.4%)	Non-CS grp: Data available for 2382 pts at 3 mos, 1547 at 6 mos, 1374 at 12 mos, 826 at 18 mos, and 481 at 24 mos. Pts undergoing >1 type of epilepsy surgery were excluded from subgrp análisis. *Outcome measures:* Reduction in seizure frequency; QOL	non-CS grp (%pts): *At 12 mos:* ≥50%: 47.6%, 58.0% (NS) ≥75%: 28.5%, 37.1% (*P*=0.002) Seizure-free: 4.1%, 6.9% (NS) *At 24 mos:* ≥50%: 55.1%, 62.2% (NS) ≥75%: 31.4%%, 43.7% (*P*=0.018) Seizure free: 5.1%, 8.3% (NS) Statistically significant improvements in all areas of QOL between non-CS and CS grp at 3 mos; at 24 mos only difference in alertness (*P*=0.042). *Complications:* NR	and a large # of pts w/ prior epilepsy surgery improved. Therefore, VNS may be an option for pts who do not sufficiently respond to surgery. *Limitations:* Retrospective analysis of pt registry data; registry participation is voluntary, therefore there may be some bias; # of pts differs among f/u dates; lack of blinding; substantial missing data. *Quality:* Good (upgraded because of very large sample size, presence of comparator grp)
Nei et al. (2006) Jefferson Medical College, Philadelphia, PA Prospective nonrandomized comparative study to evaluate efficacy and safety of corpus callosotomy and VNS in pts w/ refractory generalized seizures *F/u:* Mean 4.5 yrs for corpus callosotomy pts; mean 1.3 yrs for VNS pts *Time frame:* 1988-2001	n=78 pts w/ intractable epilepsy Corpus callosotomy grp: n=53 pts (36 male, 17 female; 38% partial, 62% generalized epilepsy) VNS grp: n=25 pts (15 men, 10 women; 64% partial epilepsy, 36% generalized epilepsy) VNS grp had significantly longer duration of epilepsy than corpus callosotomy grp (mean 32 vs 23 yrs). *Inclusion criteria:* All pts had refractory epilepsy w/ GTC, secondarily GTC, tonic, or atonic seizures, which were uncontrolled despite a trial of >3 AEDs *Exclusion criteria:* Any focal resective procedure or multiple	53 pts were tx'd w/ corpus callosotomy; 25 pts received implanted VNS tx. *Outcome measures:* Reduction in seizure frequency (mean # seizures/mo); proportion of pts w/ ≥50% or ≥80% seizure reduction	*Corpus callosotomy results (% pts):* Generalized tonic-clonic seizures (≥50% decrease in seizure frequency): 79.5% Partial epilepsy pts: 82% had ≥50% seizure reduction. Generalized epilepsy pts: 78% had >50% seizure reduction; 60% had ≥80% reduction *VNS pts:* Generalized tonic-clonic seizures (≥50% seizure reduction): 50% Partial epilepsy pts: 71% had ≥50% seizure reduction Generalized epilepsy pts: 20% had ≥50% seizure reduction; 33% had ≥80% seizure reduction NS differences between grps in proportion of pts achieving ≥50% or ≥80% reduction in seizure frequency. If all seizure types were combined, significantly more pts achieved ≥50% reduction in seizure	Results suggest that both tx modalities were effective, w/ complications more serious for corpus callosotomy pts. Overall, corpus callosotomy was more effective than VNS in reducing seizure frequency, but there was no difference when seizure types were analyzed separately. However, the sample sizes were very small for VNS and for different seizure types. *Limitations:* Lack of control grp; shorter mean f/u of VNS grp; lack of randomization and blinding; small sample size for VNS grp; small sample size for seizure type comparisons. *Quality:* Poor (downgraded

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	subpial transection procedure for epilepsy in addition to the corpus callosotomy; pts w/ partial data		frequency for corpus callosotomy (79%) vs VNS (40%) (*P*<0.001). *Complications (corpus callosotomy, VNS):* Overall (21%, 8%); permanent (3.8%, 0%) Serious complications (# pts): Death (1, 0); status epilepticus (1, 0); gait difficulty (2; 0); osteomyelitis (1, 0); hemiparesis (2, 0); disconnection syndrome (2, 0); deep venous thrombosis (1, 0); defective battery (0, 1); site infection (0, 1) (transient complications NR)	from fair due to small VNS grp sample size, differences in f/u duration between both grps, and differences in duration of epilepsy prior to tx).
McGlone et al. (2008) Queen Elizabeth II Health Sciences Centre Halifax, Halifax; the Ottawa Hospital, Ottawa, ON; University of Sasketchewan, Saskatoon, Canada Prospective nonrandomized study using matched controls to evaluate QOL following VNS for epilepsy *F/u:* 12 mos *Time frame:* NR *Funding source:* A health plan paid for some of the devices	n=35 pts VNS grp: n=16 (mean age 35 yrs; 9 male, 7 female) Medical grp: n=9 (mean age 37 yrs; 3 male, 6 female) Surgery grp: n=10 (mean age 36 yrs; 4 male, 6 female) *Inclusion criteria:* Pts w/ epilepsy; age >16 yrs; pts w/ developmental delay or comorbid psychiatric condition were permitted; medically incontrollable complex PS for ≥5 yrs; no progressive neurological disorder had caused epilepsy; did not meet criteria for surgical resection or callosotomy *Exclusion criteria:* NR	VNS grp received implantable VNS. Stimulator activated on implantation. Current was adjusted from 0.25 – 3.0 mA over several wks (pulse width, 500 μsecs; frequency, 30 Hz; stim on 30 secs, stim off 5 mins). Changes in medication were permitted. Medical grp received standard medication. Surgery grp underwent cerebral resection of the anterior temporal lobe (8 pts), selective amygdalohippocampectomy (1 pt), or functional hemispherectomy (1 pt). *Outcome measures:* QOL (QOLIE-89); depressive affect (Geriatric Depression Scale); memory (MOQ-SA, MOQ-SB, MOQ-RA, MOQ-RB, WMS-III)	3/16 (18.8%) pts in VNS grp were responders, defined as ≥50% reduction in seizure frequency; 11/16 (69%) had some reduction in seizure frequency. Reduction in seizure frequency did not correlate w/ QOL. QOLIE-89 (*P*<0.005) and MOQ-SA values (*P*<0.05) improved from baseline. Other MOQ scales did not improve. NS difference among grps. Surgery grp improved more than VNS grp and medication grp in QOL. *Complications:* NR	Results suggest that VNS does not substantially improve QOL compared w/ resective surgery and medical tx. Additional studies are needed to confirm these results. *Limitations:* Lack of randomization; sample size too small to detect small to moderate differences; heterogeneous VNS pt grp; changes in medication not controlled; QOLIE-89 designed to capture medication-related complications. *Quality:* Poor (downgraded because of small sample size)
Sherman et al. (2008) Alberta Children's Hospital, University of Calgary, Calgary; British Columbia's Children's Hospital, University of British Columbia, Vancouver, Canada	n=53 pts *VNS grp:* n=34 (mean age 12.3 yrs; range 3-18; 20 male, 14 female) *Control grp:* n=19 pts (mean age 9.5 yrs, 4-14; 10 male, 9 female)	Following VNS implantation, output current was increased to ≤2.0 mA (30 secs stim on, 5 mins stim off). Neurological assessment performed monthly until maximum setting reached,	Pts in control grp were younger than those in VNS grp. VNS and control grp (points) (mean values ± SD): *ICNDS:* Baseline: 22.6±7.3; 11.1±8.5 Retest: 19.8±8.8; 14.1±8.3	Results suggest that VNS did not significantly improve QOL in most pts. Pts who had ≥50% improved seizure frequency did not show more improvements in QOL than nonresponders. However, the sample sizes may have been

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Prospective, nonrandomized, controlled study to evaluate QOL in VNS for epilepsy *F/u:* 12 mos *Time frame:* 1999-2003 *Funding source:* British Columbia Medical Services Foundation/Vancouver Foundation	*Inclusion criteria:* VNS grp pts w/ epilepsy intractable to antiepileptic drugs; either ineligible for or failed epileptic surgery *Exclusion criteria:* NR *Clinical hx (VNS, control):* Etiology: Tumor (6%, 5%); vascular (0, 21%); infection (21%, 5%); dysplasia (112%, 16%); cryptogenic or unknown (29%, 43%), LGS or West syndrome (15%, 0); metabolic (12%, 0); mesial temporal lobe sclerosis (3%, 11%)	then at 6 and 12 mos. Cognitive assessment, QOL, behavior, adaptive functioning 1 mo prior and 1 yr postimplantation. *Outcome measures:* QOL (ICNDS, Global QOL); neurological assessment; cognitive assessment; behavior; adaptive functioning; seizure frequency	*Global QOL:* Baseline: 3.5±1.4; 4.4±1.5 Retest: 3.6±1.3; 4.4±1.2 Baseline levels differed between both QOL measures (P<0.0001). QOL in VNS and control grp (% pts): *ICNDS:* Decreased: 14%, 37% (NS) Unchanged: 52%, 53% (NS) Increased: 33%, 11% (NS) *Global QOL:* Decreased: 9%, 11% (NS) Unchanged: 77%, 83% (NS) Increased: 14%, 6% (NS) Outcomes in responders and nonresponders in VNS grp (points ± SD): # pts: 14, 20 ICNDS: 19.5±9.6; 20.8±7.8 (NS) Global QOL: 3.8±1.5; 3.5±1.2 (NS) Reduction in seizure frequency in VNS pts (% pts): >90%: 6% 70%-90%: 21% 50%-70%: 12% <50%: 56% *Complications:* NR	too small to detect a small to moderate difference. *Limitations:* Lack of randomization; small sample size; lack of sham control; heterogeneity between grps (e.g., VNS grp had lower baseline QOL). *Quality:* Fair
Uncontrolled clinical trials				
Penry & Dean (1990); Uthman et al. (1990); Uthman et al. (1993) Veterans Administration Medical Center, Neuroscience Institute of Santa Fe; University of Florida College of Medicine, Gainesville, FL; Bowman Gray School of Medicine, Winston-Salem, NC	n=14 pts (age 18-58 yrs) *Inclusion criteria:* Pts w/ medically intractable partial (complex, simple, or both) seizures; >6 seizures/mo, seizure free period ≤2wks; ≥1 yrs baseline seizure counts *Exclusion criteria*: Status epilepticus in previous 2 yrs; treatable underlying etiology; progressive neurologic or systemic	52-wk baseline seizure hx before NCP implantation. Each pt served as own control: 4 wks no stim, 8 wks stim, 4 wks no stim, 8 wks stim. *Outcome measures*: Change in seizure frequency, duration, intensity, type; magnet use and effect; complications	Pooled data from #E0 and #E02 studies. Mean reduction in seizure frequency 46.6% after 14-35 mos (range, 0% to 100%); 5/14 (36%) pts had ≥50% reduction in seizure frequency during active stim times. *Complications:* Transient hoarseness, hiccups, and muscle spasms; no cardiac or gastrointestinal effects.	Results indicate that VNS may reduce seizure frequency. In 36% of the pts, seizures were reduced by >50% during stim period of the trial compared w/ no-stim intervals. *Limitations:* Small sample size; lack of control grp; although blinded, pts probably were able to distinguish

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VNS Study #E01, #E02; multicenter, single-blind, uncontrolled, phase I trial *F/u*: Mean 25 mos (range, 14-35 mos) *Time frame*: NR *Funding source:* Cyberonics Inc.	disorders; mental retardation; drug abuse; asthma; gastritis; gastric or duodenal ulcers; insulin-dependant diabetes; prior vagotomy			between stim and no-stim periods, therefore, potential for placebo effect exists. *Quality:* Poor
George et al. (1994); Salinsky et al. (1996) First International Vagus Nerve Stimulation Study Group centers VNS Study #E03; multicenter, randomized, parallel, double-blind, prospective study of long-term effects of high-frequency VNS; ITT analysis used to prevent bias resulting from exclusion of dropouts *F/u:* 12 mos *Time frame*: NR *Funding source:* Cyberonics Inc.	n=114 pts (age 14-57 yrs) *Inclusion criteria:* Pts w/ medically intractable partial epilepsy; same population as previous study *Exclusión criteria:* NR	3-mo baseline seizure hx before implantation w/ NCP. Pts randomly assigned to high-stim or low-stim levels for 14 wks followed by indefinite open-extension phase in which all pts received high-level VNS. *Outcome measures:* Change in seizure frequency; complications	14 pts discontinued tx before 12 mos (lack of efficacy, n=9; other reasons, n=5). Seizure frequency reduced by 20% in 1st 3 mos of VNS and by 32% after 1 yr. 31/100 (31%) pts who completed 12 mos had ≥50% reduction in seizures. Response in 1st 3 mos predictive of long-term response. *Complications:* Some transient complications reported in 11 pts.	Results suggest that pts who responded to initial VNS were likely to continue to respond. *Limitations:* Controlled study only lasted 14 wks; adequacy of low-level stim as placebo unproven; pts who dropped out due to lack of efficacy not included in 12-mo tx analysis. *Quality:* Fair (downgraded from high because study lacked controls after 14 wks tx)
Murphy et al. (1995); Hornig et al. (1997) Children's Mercy Hospital, Kansas City, MO Prospective case series of VNS in children *F/u:* 2-14 mos (range)	n=19 children (age 4-19 yrs) *Inclusion criteria:* Children w/ medically and surgically intractable seizures *Exclusion criteria:* NR	1-mo baseline seizure hx before implantation w/ NCP; stim at therapeutic levels started 2 wks after implantation. *Outcome measures:* Seizure frequency; overall status on global rating scale; number of antiepileptic drugs required;	Pts evaluated monthly for 1st 3 mos after activation and every 3 mos thereafter; range of f/u 2-30 mos. 6/19 (32%) had >90% reduction and 10/19 (53%) had >50% reduction in seizure frequency. 13/19 (68%) showed improvement in overall status on global evaluation scores; 5 pts unchanged; 1 pt worsened. 5/19 (26%) pts able to reduce number of antiepileptic drugs.	Results suggest that VNS was effective in controlling intractable seizures in some children. Degree of improvement was greater in children than adults. VNS may also be beneficial for pts w/ LGS, and pts who had previous corpus callosotomy.

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Time frame: NR		complications	All 3 children who had not responded to corpus callosotomy improved w/ VNS and 5/6 pts w/ LGS had 90% reduction of seizures. *Complications (# pts):* Wound infection (2); generator failure (1); hoarseness during stim (all pts)	*Limitations:* Small and heterogeneous sample; no control grp; short baseline period; variable f/u. *Quality:* Poor
Lundgren et al. (1998) University Hospital of Lund, Lund; Karolinska Hospital, Stockholm, Sweden Prospective longitudinal study of VNS in children *F/u:* 12-24 mos *Time frame:* NR	n=16 children (10 boys, 6 girls; age 4-18 yrs) *Inclusion criteria:* Children age ≤18 yrs w/ medically and surgically intractable seizures *Exclusion criteria:* NR	6-mo baseline seizure hx obtained before implantation of NCP; all pts tx'd w/ therapeutic level of VNS for 12-24 mos. *Outcome measures:* Change in seizure frequency; seizure severity; global evaluation of QOL; complications	After 10-12 mos of VNS, 6/16 (37%) pts had 50% reduction in seizure frequency, w/ reduction in seizure severity and QOL. Stimulators were turned off in 5 pts due to lack of efficacy. *Complications (# pts):* Hoarseness (6); neck pain (1); aspiration (2); electrical transmission problem (6)	Results suggest that VNS had a benefit in some pts; however, reduction in seizure frequency was not as marked as in some other studies involving children. The side effects of aspiration and multiple electrical transmission problems are a cause for concern. *Limitations:* Small and heterogeneous sample; lack of control grp. *Quality:* Poor
Amar et al. (1999) University of Southern California, Los Angeles, CA; Cyberonics, Inc., Houston, TX VNS Study #E05; multicenter, randomized, parallel, double-blind, prospective study to compare high-level w/ low-level VNS. VNS Study Arm #XE5; open-label, nonblinded extension trial *F/u:* 15 mos *Time frame:* NR *Funding:* Cyberonics Inc.	n=195 pts (age 13-60 yrs) randomized to: High-stim grp: n=94 Low-stim grp: n=102 *Inclusion criteria:* Pts who were previously enrolled in VNS Study #E05; pts aged >12 yrs w/ medically refractory complex PS *Exclusion criteria:* Prior cervical vagotomy, VNS, or resective epilepsy surgery	After 3-mo baseline period, pts implanted w/ NCP, then followed for 3 mos. High-stim: 30 Hz, 500 μsec × 3 mos Low-stim: 1 Hz, 130 μsec × 3 mos (VNS Study #E05). For VNS Study #XE5, all pts received high-stim × 15 mos. Physicians were allowed to change stim parameters. *Outcome measures:* Seizure frequency; adverse events; QOL measures	After 15 mos total stim, pts had a mean reduction in seizures of 37%. 39% had >50% reduction in seizures, 21% had >75% reduction, 2% remained seizure free. Statistically significant improvement of QOL at 6 and 12 mos. 21 pts discontinued due to lack of efficacy or by pt decision; 3 pts experienced adverse events; 1 pt was lost to f/u; 2 pts died from causes unrelated to VNS. *Complications:* Transient voice alterations during stim (56%); unspecified pain (20%); headache (16%)	Results suggest that VNS is safe and effective. Efficacy was maintained or slightly increased throughout duration of study (15 mos). An analysis that adjusted for dropouts and missing data was made w/ similar results, thus selection bias is unlikely. *Limitations:* No control grp in extension trial; 11% dropout rate. *Quality:* Fair for seizure frequency (downgraded from good because there was no control grp beyond 14 wks tx); poor for QOL

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Ben-Menachem et al. (1999) Göteborg University, Göteborg; Dicamed Inc., Stockholm, Sweden Prospective, open, uncontrolled, single-center, longitudinal study of VNS w/ long-term analysis of epilepsy subgrps PS, PGS, and LGS *F/u:* Mean f/u 20 mos (range 3-64) *Time frame:* 1992-1997	n=64 pts PS grp: n=47 PGS grp: n=9 LGS grp: n=8 *Inclusion criteria:* Medically and surgically intractable seizures or if surgery was not indicated *Exclusion criteria:* Change of AEDs during study	Stim parameters: Standard parameters w/ 1.0-1.5 mA; w/ unsatisfactory seizure control, rapid-stim parameters used at 7 secs stim on and 12 secs stim off. *Outcome measures*: % change in seizure rates during last 3 mos of tx and after an average of 20 mos stim (range 3-64) compared w/ 3-mo preimplantation baseline; seizure severity	40.4% (19/47) pts w/ PS had >50% reduction, 17% (8/47) reported >75% reduction, and 21/47 (44.7%) were nonresponders. 7/49 (14.3%) reported seizure reductions between 10% and 49%. Responders experienced >50% reduction of seizure severity. 4/8 (50%) pts w/ LGS had >50% seizure reduction. 5/8 (62.5%) pts w/ PGS had >50% seizure reduction, and 4/8 (50%) experienced >75% seizure reduction. *Complications (# pts):* Hoarseness (11); paresthesia (1); dyspnea (1); death in status epilepticus (3) and SUDEP (1); cord paresis (1); throat pain (3).	Results suggest that VNS can provide long-term reduction in seizure frequency in some pts dx'd w/ PS, PGS, and LGS. *Limitations:* No control grp; small sample size for PGS and LGS; variable VNS tx time; lack of correlation analysis of VNS tx time and seizure frequency reduction. *Quality:* Poor
Labar et al. (1999) New York Presbyterian Hospital-Cornell Medical Center, NY, NY; Mercy Children's Hospital, Kansas City, MO; University of California at San Diego, La Jolla, CA VNS Study #E04; prospective, multicenter, open-label trial to evaluate VNS in pts w/ generalized seizures (subgrp analysis) *F/u*: 3 mos *Time frame:* NR *Funding source:* Cyberonics Inc.	n=24 pts (age 4-40 yrs) *Inclusion criteria:* ≥1 seizure per mo; age >3 yrs; no cardiac or progressive neurological disease; subset of pts of #E04 trial w/ generalized seizures and only generalized epileptiform activity or generalized slowing on EEG *Exclusion criteria:* NR	After 1-mo baseline period, pts were implanted w/ NCP and followed × 3 mos. Pts evaluated in this study received high-stim (30 Hz, 500 μsec) *Outcome measures*: Seizure frequencies determined during 1-mo baseline and 3-mo postop f/u; complications recorded at time of implantation and 1-3 mos f/u	VNS produced 46% median reduction in seizure rate compared w/ baseline period. 66.7% of pts experienced median seizure reductions >30%, and 45.8% of pts experienced median seizure reductions of 50%. Baseline seizure rate accounted for 49.6% of variability. Higher baseline seizure rates and older age at epilepsy onset predicted better reduction in seizure rates. *Complications (1-3-mo f/u) (# pts):* Cough (6); abdominal pain (2); incisional paresthesias (2); incisional pain (2); anorexia (1); hiccups (1); dysphagia (1); emesis (1); fatigue (1)	Results suggest that VNS is safe and effective for at least 3 mos for pts w/ generalized epilepsy. High baseline seizure rates and older age at epilepsy onset may be predictors for VNS efficacy. *Limitations:* No control grp; sample size too small to allow for analysis of differences between types of generalized epilepsies; short f/u time and short baseline period. *Quality:* Poor
Morris et al. (1999) Medical College of Wisconsin, Milwaukee, WI Open-label, long-term	n=454 pts *Inclusion criteria:* Pts w/ medically intractable partial (complex, simple, or both) seizures; all pts previously	Stim parameters as described for VNS studies #E01-#E05; adjustments of stim parameters allowed after active trials completed. No	440/454 pts yielded assessable data. % of pts w/ >50% median seizure reduction: 3 mos: 23% Yr 1: 37%	Results suggest that there was efficacy and safety of VNS for a tx period of up to 3 yrs. Results show significant continued decrease in seizure

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efficacy, and safety/tolerability study of VNS in pts w/ refractory epilepsy *F/u:* 3 yrs *Time frame:* 1988-1997 *Funding source:* Cyberonics Inc.	enrolled in VNS studies #E01-#E05; of these, 25 pts dx'd w/ PGS (#E04) *Exclusion criteria:* NR	restrictions were placed on concomitant AED use. F/u: Assessed every 6 mos. *Outcome measures:* Seizure frequencies; medication usage; complications	Yr 2: 43% Yr 3: 43% Magnitude of increase in efficacy significant for 3 mos to 2 yrs. Continuation rates declined from 97% at yr 1 and 85% at yr 2 to 72% at yr 3. Most common reason for discontinuing was inefficacy of tx. *Complications*: Total of 9 deaths, of which 4 were classified as SUDEP. There was a statistically significant decrease of the following side effects observed at yrs 1, 2, and 3, respectively, including paresthesia (12%, 4%, 0%); cough (7.8%, 5.9%, 1.6%); hoarseness (29%, 19%, 2%); and shortness of breath (8%, 3%, 3%).	frequencies up to 2 yrs. Pt-reported side effects significantly decreased over 3-yr f/u. *Limitations:* No controls; no restrictions on AED use and NCP settings. *Quality:* Poor
Murphy (1999) Children's Mercy Hospital, Kansas City, MO Multicenter, retrospective study of VNS in pediatric population using databases available from prospective, controlled VNS studies #E01-#E05 *F/u:* 18 mos *Time frame:* NR *Funding source:* Cyberonics Inc.	n=60 children (age 3.5-18 yrs) *Inclusion criteria:* Children w/ medically refractory epilepsy who were previously enrolled in #E01-#E05 VNS studies *Exclusion criteria:* NR	All pts followed at 4-12 wks baseline and for at least 3 mos; AEDs not changed. #EO3, #E05 pts randomly assigned to high stim (30 Hz, 500 μsec) or low stim (1 Hz, 130 μsec) settings; #E04 trial participants received high-stim. *Outcome measures:* Seizure rates; QOL; complications	Median seizure frequency reductions: 3 mos (n=60): 23% 6 mos (n=55): 31% 12 mos (n=51): 34% 18 mos (n=46): 42% Benefit in children age <12 yrs similar to whole grp. *Complications (% pts):* 0-3 mos: Fever (26.7%); coughing (25.0%); headache (23.3%); colds (20.0%); voice alteration (21.7%); infection (18.3%); vomiting (18.3%); pharyngitis (13.3%); nausea (11.7%); 12-18 mos: voice alterations (13.0%); increased tolerance to side effects over time. Other complications, occurring in <10% pts, included: aspiration, pneumonia, necrosis of skin overlaying generator.	Results suggest that VNS may be an effective adjunct tx for epilepsy in pediatric pts. Age was not a predictor of efficacy in this study. Efficacy increased over time. *Limitations:* Retrospective analysis; data obtained from several trials; stim conditions differed somewhat between trials; no placebo control in #E04. *Quality:* Fair (upgraded from poor because data are prospectively gathered from well designed trials and reporting on moderate time frame)
Parker et al. (1999) Guy's Hospital; King's College Hospital, London; Leeds General Infirmary, Leeds, UK	n=16 children (age 5-16 yrs) *Inclusion criteria:* Pts w/ cryptogenic epileptic encephalopathy, defined as	Seizure frequency recorded for ≥8 wks before NCP implantation; f/u for 1 yr after device implantation	Median seizure frequency reduction at 0-6 and 6-12 mos was 19% and 17%, respectively (NS). After 2 yrs of VNS, median % of seizure reduction was significant (43%). 1 pt was seizure free; 5/15 had >60% and 3/15 had	Results suggest that there is some supporting evidence for the efficacy of VNS as an adjunct tx in children dx'd w/ epileptic encephalopathy;

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
Prospective, uncontrolled, open-label study of VNS in epileptic encephalopathy *F/u*: 12 mos *Time frame*: NR	occurrence of mixed generalized seizures w/ diffusely slow EEG w/ generalized or multifocal interictal paroxysmal abnormalities *Exclusion criteria:* NR	*Outcome measures:* Seizure type and frequency assessed by parents' description of seizures in a diary; EEG recording at baseline, 6, and 12 mos; QOL and behavioral assessment by questionnaire conducted before and 1 yr postimplantation	>40% seizure reduction compared w/ baseline. EEG measurements did not reveal any improvement in background, focal, or generalized discharges. Behavioral scores improved significantly but were not correlated w/ seizure frequency. Other QOL measures did not show significant improvement. *Complications*: 1 device removed due to postop infection	however, seizure frequencies were not significantly reduced, and the EEG diagram did not improve during the first yr of VNS. Pts experienced statistically significant seizure reductions only during the second yr of VNS. The authors report that changes in AED or stim parameters alone could not account for these improvements. *Limitations:* No control grp; small and heterogeneous sample; 2-yr data provided as addendum to published article. *Quality:* Poor
DeGiorgio et al. (2000) Multicenter study involving 24 locations in U.S. VNS Study #E05; VNS Study Arm #XE5; open-label extension trial *F/u:* 12 mos *Time frame:* NR *Funding source:* Cyberonics Inc.	n=195 pts randomized to: High-stim grp: n=94 Low-stim grp: n=102 *Inclusion criteria:* Pts who were previously enrolled in VNS Study #E05; ≥6 complex PS or GTC seizures per mo *Exclusion criteria:* Prior cervical vagotomy, VNS, or resective epilepsy surgery	After 3-mo baseline period, pts implanted w/ NCP, then followed × 3 mos. Pts randomly assigned to: High-stim: 30 Hz, 500 μsec × 3 mos Low-stim: 1 Hz, 130 μsec × 3 mos (VNS Study #E05). For VNS Study #XE5, all pts received high-stim × 15 mos. Physicians allowed to change stim parameters. *Outcome measures:* % reduction in total seizure frequency at 3 and 12 mos after completion of acute #E05 trial, compared w/ preimplantation baseline;	See Amar et al. (1999). 164/195 (84%) pts completed 12-mo f/u; pts discontinued due to adverse events (2), deaths (2), loss to f/u (1). *Outcome measures (3 mos, 12 mos):* Median reduction in total seizure frequency (vs preimplantation baseline): 34%, 45% >50% reduction in total seizure frequency: 34%, 35% >75% reduction in total seizure frequency: 16%, 20% 33/195 pt experienced <25% reduction in total seizure frequency; >50% increase was observed in 3% of pts. Trend toward correlation between reduction in seizures and increased current NS (*P*=0.056). *Complications (3 mos, 12 mos):* Accidental	Results suggest that VNS significantly reduced seizure frequency in some pts w/ complex partial or generalized seizures. Efficacy of VNS improved significantly over time. No increase of VNS-related side effects occurred. Hoarseness, cough, and pain were generally improved after adjustment of device parameters. *Limitations:* No control grp; 16% dropout rate. *Quality:* Fair (downgraded from high because there was no control grp beyond 14 wks tx)

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		between-grp analysis low-stim vs high-stim VNS during #E05; device settings; between-grp analysis of safety data, QOL scores, complications	injury (9%, 15%); cough (21%, 15%); voice alteration (62%, 55%); dyspnea (16%; 13%); pain (17%, 15%); paresthesia (25%, 15%); headache (20%, 16%); pharyngitis (9%, 10%); depression (3%, 5%); infection (4%, 6%); 2 reported deaths, 1 classified as SUDEP	
Hosain et al. (2000) New Presbyterian Hospital, Cornell University, NY, NY. Prospective case series of VNS in pts dx'd w/ LGS *F/u:* 6 mos *Time frame:* NR	n=13 pts (age 4-44 yrs) *Inclusion criteria:* Severe medically refractory mixed seizures, static encephalopathy, and generalized slow spike-and-wave discharges *Exclusion criteria:* NR	After 1-mo baseline period, NCP implanted; stim intensity adjusted to maximum level tolerated by pts. *Outcome measures:* Median seizure rates over first 6 mos after NCP implantation vs baseline seizure rates; changes in AED use	During 1st 6 mos of VNS, statistically significant median seizure frequency reduction of 52% observed. % reduction of seizure frequency at 6 mos f/u: >90%: 23% (3/13) >75%: 15% (2/13) >50%: 7.7% (1/13) ≥25%: 46% (6/13) No improvement: 7.7% (1/13) Change in AED use NS after 6 mos compared w/ baseline period. However, total # of drugs could be reduced by ≥1 AED after 2 mos of VNS in 46% (6/13) of pts. *Complications (# pts):* Excessive coughing (3); incisional infection (1)	Results suggest efficacy of VNS for some pts dx'd w/ LGS. Results indicate that, for some pts, VNS may reduce # of AEDs needed. *Limitations:* No control grp; small, heterogeneous study sample; stim intensity varied between pts; other stim parameters not constant during last 3 mos of trial period. *Quality:* Poor
Sirven et al. (2000) Mayo Clinic, Scottsdale, AZ 16 centers in U.S. Retrospective and prospective study using data from randomized blinded active-control VNS studies #E03, #E05, and open-label study #E04 *F/u:* 1 yr *Time frame:* NR *Funding source:* Cyberonics Inc.	n=45 pts randomly assigned to: High-stim grp: n=94 Low-stim grp: n=102 *Inclusion criteria:* Age ≥50 yrs w/ medically intractable seizures w/ frequency ≥6 complex partial or secondarily generalized convulsive seizures per mo *Exclusion criteria:* Prior cervical vagotomy, VNS, or resective epilepsy surgery	All pts had 12-16 wks baseline period; AEDs not changed. High-stim: 30 Hz, 500 μsec Low-stim: 1 Hz, 130 μsec #E04 trial participants received high-stim similar to #E05 high-stim settings. *Outcome measures:* Seizure frequency; QOL scores; complications	Data available for 45 pts at 3 mos and 31 pts at 1 yr. At 3 mos post-NCP implantation, 27% of pts reported seizure frequency reductions >50%. After 12 mos f/u, 67% of pts experienced seizure frequency reductions >50%. QOL scores improved significantly over time. *Complications (# pts):* Coughing (16); chest or arm pain (12); paresthesias (7); dyspnea (4); dyspepsia (2); dizziness (2); insomnia (1); headache (2); 1 death unrelated to VNS tx	Results suggest that VNS was effective and well tolerated in pts >50 yrs of age. Side effects were mild and similar to those observed in younger pts. *Limitations:* Analysis did not include pts of low-stim grp as active control grp for seizure-frequency outcome; lack of control for tx beyond 14 wks. *Quality:* Fair (downgraded from good because there was no control grp for tx beyond 14 wks)
Helmers et al. (2001) Hacettepe University	n=125 children	After 2-mo baseline period, NCP implanted and seizure	F/u data available for 95, 56, and 12 pts at 3, 6, and 12 mos, respectively.	Results suggest efficacy of VNS in pediatric pts dx'd w/

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Children's Hospital, Ankara, Turkey; 7 U.S. medical centers Retrospective analysis of VNS in children w/ medically refractory epilepsy *F/u:* 12 mos *Time frame:* December 31, 1998 – March 31, 1999 *Funding source:* In part by Cyberonics Inc.	*Inclusion criteria:* Age ≤18 yrs w/ medically refractory epilepsy *Exclusion criteria:* NR *Clinical hx (%pts):* Most common seizure types: PS (47%), generalized (18.5%), LGS (34.5%)	diaries maintained by caregiver; seizure diaries reviewed w/ investigator. QOL parameters assessed using nonvalidated 5-point scale. *Outcome measures:* Seizure frequency and QOL at 3, 6, and 12 mos; complications	Average reduction in seizure frequency significant, decreasing by 36.1% and 44.7% at 3 and 6 mos, respectively. Pts age ≤6 or ≤12 yrs responded similarly to the grp as a whole. Among pts w/ LGS, mean seizure reduction was 26.6% at 3 mos and 47.1% at 6 mos. QOL parameters improved in alertness, verbal communication, school performance, clustering of seizures, and postictal periods. *Complications:* Voice alterations (57.9%); coughing (37.9%); ear pain (1.1%); increased drooling (<1%); moderate to severe dysphonia (1 pt); right-sided weakness and incoordination (1 pt); broken electrodes (3 pts)	partial or generalized seizures, and LGS. Reductions were similar to those in other reports. Changes in AED use did not appear to affect seizure rates. *Limitations:* Retrospective, uncontrolled, nonrandomized study. *Quality:* Poor
Majoie et al. (2001) Epilepsy Center Kempenhaeghe, Heeze; University Hospital of Maastricht and Maastricht University, Maastricht; University Medical Center St. Radboud, Nijmegen, the Netherlands Prospective, open-label study of VNS in epilepsy pts dx'd w/ LGS *F/u:* 24 mos *Time frame:* NR	n=16 pts (age 7-18 yrs) *Inclusion criteria:* LGS-type seizures; 1st/2nd choice AED ineffective or resulting in side effects; not candidates for surgery; disturbed occipital activity and slow spike waves; moderate to mild mental handicap *Exclusion criteria:* Progressive neurodegenerative disease; ill health contraindicated surgery; severe obstructive pulmonary disease; severe disturbance of cardiac rhythm; severe stomach disorder	After 6-mo baseline period, NCP was implanted. Stim parameters were stim on 30 secs, stim off 3 mins, pulse width 500 μsec, and output current titrated to 1.5-2.0 mA. No change in parameters during 1st 3 mos, then switch to 7 secs stim on and 18 secs stim off permitted. F/u: At 6, 12, 18, and 24 mos following surgery. *Outcome measures:* Seizure frequency and severity; neuropsychological outcome measures (cognitive and QOL); cost-effectiveness	At 6 mos after NCP implantation, seizure frequency increased in 1 (6%) pt, no change in 3 (19%) pts, decreased by 30%-50% in 5 (31%) pts, and decreased by >50% in 3 (19%) pts; 1 (6%) pt remained seizure free. Significant reduction in seizure severity was observed. Cognitive function (mental age, language, motor function, attention, cognitive style) did not improve significantly. QOL (independence, behavior, PDD characteristics, mood) did not significantly improve, w/ exception of mood. Improvement was independent of seizure control. VNS resulted in cost reduction of $2722/yr/pt. *Complications:* Tingling sensation in throat (31%, 5 pts); coughing (38%, 6 pts); hoarseness (38%, 6 pts)	Results suggest that VNS may be effective for pts dx'd w/ LGS. Reduction in seizure frequencies was lower than that reported for VNS studies #E01-#E05 and other reports. Difference may be due to longer baseline period in this study vs previous report. Longer baseline period may give a more accurate estimate of mean seizure frequencies. Changes in neuropsychological parameters appear to be independent of seizure control; therefore, VNS may directly affect neuropsychological parameters. *Limitations:* Open-label study; no control grp; stim

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				parameters not constant; small sample size. *Quality:* Poor
Scherrmann et al. (2001) University of Bonn, Bonn, Germany Prospective, open-label clinical study on seizure outcome in adult epilepsy pts under VNS, w/ embedded randomized, active tx comparison trial of stim parameters *F/u:* Mean 15.8+10.3 mos *Time frame:* February 1998 – May 31, 2001	n=95 adult pts; 85 included in data analysis *Inclusion criteria:* Adults; medically refractory epilepsy and ≥4 complex PS or generalized seizures per mo (n=24 for embedded, randomized, active tx comparison trial) *Exclusion criteria:* NR	Stim frequency switched from standard cycle (stim-off period 300 secs, stim-on period 30 secs, pulse width 500 μsec, frequency 30 Hz) to rapid cycle (stim-off period 30 secs, stim-on period 7 secs, pulse width 250 μsec, frequency 20 Hz) in nonresponders. *Outcome measures*: % of changes in seizure frequency per mo compared w/ baseline before implantation	No reliable f/u information from 2 pts, and 8 were still in ramp-up phase; final n=85 pts. Median 30% in seizure frequency reduction compared w/ baseline: Reduction >50%: 45% (38/85) Reduction >75%: 12% (10/85) Reduction >25%: 14% (12/85) 4 pts (5%) remained seizure free. Seizure reduction significantly increased w/ length of tx period. Rapid-cycle stim did not significantly improve seizure frequencies. *Complications:* Hoarseness (57%); cough (4%); difficulties in breathing (2%) or swallowing (4%). Surgical and postsurgical complications (# pts): Scars (3); wound infection (2); reversible pareses of left nervus recurrens (3); reversible Horner syndrome (1) 2/95 pts lost to f/u; 8 still in ramp-up phase during analysis.	Results suggest confirmation of earlier reports of the efficacy of VNS for medically refractory epilepsy. The authors claim that NCP standard settings are more effective in reducing seizure frequency than rapid stim. However, embedded, randomized, active-control trial did not confirm this observation. Almost all stim parameters changed; therefore, a meaningful interpretation of the comparison between slow and rapid cycle w/ regard to parameter optimization cannot be made. *Limitations:* No controls except in embedded, randomized, active-control trial; stim parameters altered during trial. *Quality:* Poor
Chavel et al. (2003) Yale University School of Medicine, New Haven, CT Prospective uncontrolled study of VNS for various epileptic syndromes *F/u:* 24 mos *Time frame:* NR	n=29 pts; 30 enrolled, 29 implanted, 1 pt withdrew from study *Inclusion criteria:* Age >12 yrs; medically uncontrolled partial-onset seizures w/ or w/o secondarily generalized seizures; excluded as candidates for resective epilepsy surgery; offered and accepted VNS tx *Exclusion criteria:* NR	Pts were enrolled prior to NCP implantation. NCP was activated ~2-3 wks following implantation. Standardized interviews at intake, including detailed medical hx. Changes in seizure frequency were noted as markedly decreased (≥75% reduction),	At baseline, mean total seizure frequency was 30.1/mo (range 2-123). Overall seizure frequency was significantly reduced (mean seizure frequency at baseline; 12 mos; 24 mos): GTC: 0.7; 1.2; 0.2 CPS: 21.6; 7.2; 11.3 SPS: 7.8; 5.5; 4.7 Overall seizures: 30.1; 14.0; 16.3 ≥50% reduction: NA; 54%; 61%	Results suggest that NCP reduces seizure frequency and ≥50% of pts may experience at least ≥50% reduction in overall seizure frequency. This reduction in seizure frequency may not necessarily improve neuropsychological measures such as QOL, anxiety, and

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
	Clinical hx (% pts): Seizure type: GTC (34.5%); complex PS or auras (96.5%); simple PS or auras (51.7%)	decreased (50%-75% reduction), no improvement (<50% reduction). *Outcome measures:* Changes in seizure frequency (total, GTC, complex PS frequency); self-administered instruments for neuropsychological evaluation (QOLIE-89, BAI, BDI); employment status	None of these pts was completely free of seizures at 24 mos f/u. No independent predictors of positive tx response were identified. NS changes in QOL, anxiety, and depression measures from baseline, to 12 mos, to 24 mos were noted. However, for anxiety measures, pts w/ ≥50% reduction in overall seizure frequency had a significant decrease in anxiety vs those w/ <50% reduction. Employment status improved at 12 mos from baseline and was maintained up to 24 mos. *Complications:* NR	depression. Preliminary results indicate that pts w/ decrease ≥50% seizure frequency may experience improved anxiety vs nonresponders. *Limitations:* Small sample size; lack of control grp; lack of blinded assessment; tx parameters NR. *Quality:* Poor
Holmes et al. (2004) University of Washington, Seattle, WA Prospective study to assess the outcome of VNS tx in adult pts w/ medically refractory generalized epilepsy syndrome *F/u:* 12-21 mos *Time frame:* NR	n=16 pts (mean age 36 yrs, range 22-60) w/ epilepsy *Inclusion criteria:* Dx of generalized epilepsy syndrome, either idiopathic or symptomatic; ≥6 pharmacoresistant seizures/mo for 3 mos prior to enrollment; aged ≥12 yrs; on stable regimen of ≥1 AED *Exclusion criteria:* Progressive neurologic disease; cardiac, pulmonary, or ulcer disease; cervical vagotomy; gastric surgery; mental illness; general anesthesia in prior 3 mos; using an investigational device or drug; prior VNS tx or brain stim; swallowing dysfunction; aspiration pneumonia; likelihood of hospitalization or MRI w/ body coil; ketogenic diet in prior 3 mos	Pts were followed for 3 mos preimplantation to document baseline seizure frequency. All were then implanted w/ VNS devices. Settings: 30 Hz, 500 μsec, 30 secs on, 5 mins off, magnet on at 500 μsec. Output current was adjusted to optimize response and avoid side effects. Pts were evaluated monthly. AEDs were maintained at stable pre-VNS levels. *Outcome measures:* Pt-reported or caregiver-reported reduction in seizure frequency, w/ ≥50% regarded as clinically significant.	43.8% (7/16) pts had ≥50% reduction in overall seizure frequency compared w/ baseline. 31.3% (5/16) had ≥75% reduction. 18.8% (3/6) of pts had ≥90% reduction. An additional 18.8% (3/16) reported seizures reduced by 25%-49%, and another 31.3% (5/16) reported changes ranging from decreases <25% to increases <25%. Seizure frequency increased ≥25% in 1 pt. Median % reduction in seizure frequency was significant for idiopathic (42.9%) and symptomatic (54.5%) generalized seizures. *Complications (# pts):* Voice change or hoarseness (14); throat pain w/ stim (3); swallowing complaints (2); cough (1)	Results suggest that VNS can significantly reduce seizure frequency in both pts w/ idiopathic generalized seizures and pts w/ symptomatic generalized seizures. That the drug dosages were not manipulated during the study period underscores the validity of the results. *Limitations:* Small study population; f/u interval varied, pt served as own control, relatively short baseline period. *Quality:* Poor
Labar (2004) New York Presbyterian-Cornell, New York, NY	n=269 pts (median age 32 yrs, range 2-71; 136 male, 133 female) *Inclusion criteria:* Pts undergoing	VNS tx for 1 yr w/ no change in AEDs *Outcome measures:* Effect of	Median seizure rate reduction was 45% after 3 mos of VNS (P<0.0001) and 58% after 12 mos (P<0.0001).	Results suggest that VNS reduces seizure rates and that seizure rates continue to decline during 1st yr of tx.

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
Retrospective review of VNS pt registry to evaluate pts on unchanged AEDs *F/u:* 12 mos *Time frame:* NR *Funding source:* Cyberonics Inc.	VNS for 1 yr w/o change in AEDs *Clinical hx (%pts):* Localized seizures (67%), generalizad (24%), LGS (9%), epilepsy surgery (20%)	technical parameters on seizure rates; analysis of potential predictors of response	Response to VNS was associated w/ older age (*P*=0.016), longer duration epilepsy (*P*=0.033), and syndromes other than LGS (*P*=0.003). NS differences in seizure rates between pts who received standard or rapid cycling, or changed from standard to rapid. Stim parameters did not affect seizure rates. *Complications:* NR	This decline is not related to AEDs and stim parameters. It is still not clear what factors predict a response to VNS; however, older pts and those w/ longer duration of epilepsy, as well as those w/ epilepsy syndromes other than LGS may respond better to tx. This was an exploratory study, and additional studies are needed to confirm the result. *Limitations:* Retrospective analysis of pt registry data; registry participation is voluntary, and there may be some bias; lack of blinding. *Quality:* Fair (upgraded from poor because of large sample size, prospectively defined outcomes, and research question)
Vonck et al. (2004) Ghent University Hospital, Ghent, Belgium; Dartmouth Hitchcock Medical Center, Lebanon, NH Prospective case series to evaluate efficacy of VNS in the tx of epilepsy *F/u:* Mean 33 mos (range 6-94) *Time frame:* March 1995 – February 2003	n=131 pts (mean age 32 yrs, range 4-59) *Inclusion criteria:* Medically or surgically refractory epilepsy *Exclusion criteria:* NR	All pts received implanted VNS tx. Pts were evaluated every 2-4 wks in the immediate postop period, then every 1-3 mos. *Outcome measures:* Self-reported or caregiver-reported seizure frequency	95 pts w/ complex PS w/ or w/o symptomatic generalized epilepsy had mean reduction of monthly seizure frequency of 56% (range 0-100; SD=31.2). In 18 pts w/ generalized epilepsy seizure, frequency was reduced by 49% (range 0-95; SD=32.1). *Complications (# pts):* Occasional gagging (2); stim-related hoarseness (13); infection requiring device explantation (2)	Results suggest that VNS tx is safe and can reduce seizure frequency. *Limitations:* Heterogeneous pt population; lack of explicit inclusion and exclusion criteria; not clear whether pt population included postop pts; pts served as their own controls; lack of blinded assessment. *Quality:* Poor
Huf et al. (2005) Huntington Memorial Hospital, Pasadena; Marlinda West, Lynwood,	n=40 (mean age 37 yrs, range 19-59; 21 men, 19 women) *Inclusion criteria:*	All pts underwent VNS tx. Stim was started at 1-3 wks following implantation (typical parameters: 1.0-2.0 mA, 20	1 pt died of SUDEP at 15 mos of tx, 1 pt was lost to f/u. Mean AEDs were reduced from 3.3 at baseline	Results suggest that VNS may improve QOL and reduce epilepsy-related hospitalizations in pts w/ low

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
CA Prospective, uncontrolled, open-label study of VNS in the tx of epilepsy in pts w/ IQ <70 *F/u:* 2 yrs *Time frame:* NR *Funding source:* In part by Cyberonics Inc.	Pharmacoresistant epilepsy; full-scale IQ <70 *Exclusion criteria:* NR	Hz, 250 μsec; stim on 30 secs, stim off 5 mins). *Outcome measures:* Caregiver-reported QOL and behavior (CDER); # of hospital visits; complications; changes in seizure frequency; medication use	to 2.3 at 1 yr. Mean # of seizures decreased from 5.1 seizures/mo to 3.8 seizures/mo (26% decrease). 11/40 pts (28%) had ≥50% reduction in seizure frequency. Of 4 pts, who reported clustered seizures, 3 reported improvement and 1 worsened. Both overall and individual scores of the CDER instrument demonstrated statistical improvement (n=38) at 2 yrs. Significant improvements were noted in standing balance, washing dishes, household chores, attention span, word usage, clarity of speech. Epilepsy-related hospitalizations were reduced from 40 in yr prior to VNS to 9 in yr 1, and 18 in yr 2 of VNS. *Complications (# pts):* Surgical device removal due to infection w/ successful implantation of new device (1); transient cough (NR); SUDEP (1)	IQ living in long-term care facilities and who have pharmacoresistant epilepsy. VNS may also reduce # of AEDs required to control epilepsy. *Limitations:* Uncontrolled study, heterogeneous pt population. *Quality:* Poor
Majoie et al. (2005) Epilepsy Center Kempenhaeghe, Heeze, the Netherlands Prospective cohort analysis to assess long-term efficacy of VNS tx in severe childhood epilepsy pts w/ LGS-type seizures *F/u:* 2 yrs *Time frame:* 1998	n=19 children w/ malignant childhood epilepsy resembling LGS *Inclusion criteria:* Age 7-18 yrs; different seizure types compatible w/ LGS; seizures unacceptable to pt; seizures cannot be tx'd medically; ineligible for resective surgery or callosotomy; disturbed background activity and slow spike waves on EEG; moderate or mild mental handicap *Exclusion criteria:* Fast, progressive neurodegenerative disease; poor general health contraindicating surgery; severe obstructive	All pts received implanted VNS tx. Data were collected 6 mos prior to study, and at 6, 12, 18, and 24 mos of VNS. Pts served as their own control *Outcome measures:* Caregiver-reported seizure frequency, neuropsychological outcomes (QOL; mental function)	Seizure frequency reduction of 20.6% at end of f/u period. 21% of pts showed reduction in seizure frequency ≥50%. Seizure severity showed improvement in 1st 12 mos of tx. Overall, there were NS changes in neuropsychological outcomes. *Complications (# pts):* Hoarseness (7); swallowing difficulty (1); coughing (4); tickling sensation in throat (2)	Results suggest that significant reduction in seizure frequency was achieved in this grp of pts w/ few adverse effects of tx. *Limitations:* AEDs were adjusted for some pts during the study period; small sample size; pts served as their own control. *Quality:* Poor

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
	pulmonary disease; severe disturbances of cardiac rhythm or severe stomach disorder			
Rychlicki et al. (2006) Universitá di Ancona, Ancona, Italy Prospective uncontrolled study to evaluate the clinical efficacy and safety of VNS tx *F/u:* Mean 30.8 mos (range 3-51.8) *Time frame:* NR	n=34 children (mean age 11.5 yrs, range 1.4-18; 21 boys, 13 girls) w/ drug-resistant epilepsy For measurement of neuropsychological outcomes, tx grp (n=21 pts who had been followed >18 mos) was compared w/ control grp of pts w/ epilepsy who did not receive VNS (n=21). *Inclusion criteria:* LGS; partial epilepsy w/ multiple seizure types w/ or w/o bisynchronous EEG and drop attacks; absence of progressive or systemic diseases; seizure frequency >10 per mo w/ interictal period <3 wks despite maximal drug tx regimens; epilepsy hx lasting >3 yrs or catastrophic epilepsy of infancy *Exclusion criteria:* Severe swallowing difficulties; severe self-mutilating behavior; recent-onset epilepsy; progressive metabolic or degenerative disease; congenital heart defects; gastrointestinal diseases (mainly gastroesophageal reflux); poor parental collaboration	All pts received implantable VNS tx. F/u at 3, 6, 12, 24, and 36 mos. *Outcome measures:* Caregiver-reported seizure frequency; neuropsychological outcomes (Vine adaptive behavioral scale)	Mean reduction in total seizures at f/u: 3 mos: 39% 6 mos: 38% 12 mos: 49% 24 mos: 61% 36 mos: 71% At 1 and 2 yrs, 55% and 71% of pts were considered responders, respectively. Cognitive abilities remained the same or improved in tx grp. Parental satisfaction and subjective QOL improved in tx grp. Control grp showed significant decrease in adaptive behavioral score. *Complications (# pts):* Transient pain (4); transient hoarseness and coughing (15); electrode breakage (2)	Results suggest that VNS can provide a measure of seizure control in these otherwise refractory pts. *Limitations:* Relatively small sample size; heterogeneous dx; lack of control grp for primary outcome measure; all neuropsychological outcomes NR. *Quality:* Poor
De Herdt et al. (2007) 7 centers in Belgium Retrospective study to evaluate long-term efficacy and safety of VNS for epilepsy *F/u:* ≥12 mos; mean 44 mos (range 12-120)	n=138 pts (mean age 30 yrs, range 4-59; 67 male, 71 female) *Inclusion criteria:* Pts undergoing VNS for epilepsy w/ postop f/u ≥12 mos; documented seizure rates preop and at last f/u *Exclusion criteria:* NR	VNS was initiated 2-4 wks following implantation. Stim parameters are adjusted over several wks to maximum 3.5 mA current; 30 Hz frequency; 250-500 μsecs pulse width; 30 secs stim on and 200-600 secs stim off.	Mean reduction in monthly seizure frequency was 51% (range 0%-100%). Mean seizure frequency reduced from preop was 41±61 seizures/mo (range 1-300) to 7±25 seizures/mo (range 0-120) at last f/u (P<0.001). 43% of children age ≤16 yrs had ≥50% reduction in seizure frequency compared w/ 62.4% of adults.	Results suggest that VNS reduces seizure frequency and tx effect is maintained long term. Subgrp analyses showed that children and adults receive an equal benefit and that seizure type does not influence response rates. Sample size for subgrp analysis was very small, and

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
Time frame: March 1995 – November 2005 *Funding source:* No commercial funding	*Clinical hx (# pts):* Focal epilepsy (117), generalizad epilepsy (21), LGS (13)	*Outcome measures:* Seizure frequency; changes in seizure frequency; response rates (>50% reduction in seizure frequency); subgrp analysis (seizure type, age); medication use	Response rate was 59% at last f/u and 9% were free of seizures. Response rates were similar for focal (59%), generalized epilepsy (57%) and LGS (61.5%). Mean # of AEDs preop and postop remained constant at 3 AEDs (range 1-5 vs 0-5). *Complications:* NR	additional studies are needed to confirm these preliminary results. *Limitations:* Retrospective study; lack of control; lack of blinding; small sample size for subgrp analysis; last f/u varied among pts. *Quality:* Poor
You et al. (2007) Multiple centers in Seoul, Korea Prospective, open-label, uncontrolled study to evaluate VNS for intractable multifocal or generalized epilepsy *F/u:* ≥12 mos (mean 31.4) *Time frame:* July 1999 – March 2005 *Funding source:* NR	n=29 pts (mean age 9 yrs 4 mos, range 2 yrs 5 mos – 17 yrs 10 mos; 16 boys, 12 girls; mean seizure duration 6 yrs 11 mos) *Inclusion criteria:* Medically intractable multifocal or generalized epilepsy *Exclusion criteria:* NR *Clinical hx (# pts):* Generalized seizures (17), including LGS (14), unclassified generalized seizures (2), and severe myoclonic epilepsy (1); PS (11) including pts w/ secondary GTC (10) and gelastic seizure w/ hypothalamic hematoma (1)	In 26/28 pts, medication remained stable during 1st 6 mos of study. VNS tx'd initially w/ 0.25 mA and 500 μsecs pulse width (stim on, 30 secs; stim off 5 mins). Seizure frequency was assessed at baseline, 3, 6, 12 mos, and at last f/u at ≤6 yrs. *Outcome measures:* Seizure rates; K-QOLCE; complications	Decrease in seizure rates at 3, 6, and 12 mos, and at last f/u (varied among pts) (%pts): ≥50% decrease: 57%, 75%, 71%, 54% ≥75% decrease: 32%, 36%, 36%, 32% Seizure type and etiology did not predict response rates. Improved K-QOLCE scores at 12 mos vs baseline (%pts): Memory: 32.1% Mood and alertness: 42.9% Behavior: 39.3% Achievement: 21.4% Verbal skills: 28.6% *Complications (# pts):* Hoarseness (7); dyspnea at sleep (2); wound infection (1); drooling (1); wound revision (1)	Results of this small study suggest that VNS decreases seizure frequency in pts w/ generalized and PS of various etiologies. No difference in response rates based on seizure type and etiology; however, sample size was too small to detect such a difference. Improvements in QOL were noted in some pts. Study lacked control grp, and it is not known to what extent a placebo effect may have affected outcomes. *Limitations:* Lack of control grp; small sample size; heterogeneous pt grp w/ regard to etiology; funding source not identified. *Quality:* Poor
Kabir et al. (2009) Sheffield Children's Hospital and Royal Hallamshire Hospital, Sheffield, UK Retrospective study to evaluate VNS for epilepsy in children	n=69 pts (mean age 10.3 yrs, range 3-16; 45 male, 24 female) *Inclusion/exclusion criteria:* Not defined	Pts were divided into 2 grps, based on seizure severity: Grp A (Engel I, II, and III) and Grp B (Engel IV). *Outcome measures:* Seizure severity/frequency (Engel's classification system); risk factor analysis; complications	55.08% of pts were in Grp A and 44.92% were in Grp B. NS difference between type of epilepsy, duration of tx, and outcome. NS difference between age at NCP insertion, age at epilepsy onset, time between 1st seizure and NCP implantation and outcome.	Results suggest that >50% of pts achieved improvement of epilepsy, based on Engel classification. Study did not identify any predictors of positive outcome.

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
F/u: Mean 3.9 yrs in Grp A and 3.7 yrs in Grp B (range 6 mos – 10 yrs) *Time frame:* June 1995 – August 2006 *Funding source:* NR			*Complications (# pts):* Infection (3); fluid collection around stimulator (2); lead fracture (2); difficulty swallowing (1)	*Limitations:* Retrospective study; lack of control; lack of blinding; inclusion/exclusion criteria not defined. *Quality:* Poor
Kuba et al. (2009) 6 Centers in the Czech Republic Retrospective, open-label, uncontrolled study to evaluate efficacy and safety of 5-yr VNS *F/u:* Mean 6.6 yrs *Time frame:* August 1997 – April 2002 (implantation); May-June 2007 *Funding source:* NR	n=90 pts (mean age 36.6 yrs, range 13-64; 50 men, 40 women) *Inclusion/exclusion criteria:* Not defined Clinical hx (# pts): Epilepsy surgery (23)	VNS (output current 0.5-2.25 mA; stim on, 30 secs; stim off, 1.1-5.0 mins) *Outcome measures:* Efficacy of VNS to reduce epileptic seizures at 1, 2, and 5 yrs of tx (≥50% reduction = responders); effect of magnetic stim; complications	Seizure reduction at 1, 2, and 5 yrs (% pts): Seizure free: 0, 3.3%, 5.5% ≥90%: 3.3%, 2.2%, 10% ≥50%: 41.1%, 53.2%, 48.9% Responders: 44.4%, 58.9%, 64.4% At last f/u, 38.9% of pts reported that using magnet to activate VNS at time of seizure onset suppressed seizure or reduced seizure duration. # AEDs at last f/u (%pts): ≥1 AEDs removed: 10% No change: 11.1% Increase: 76.7% *Complications (# pts):* Complication rate was 13.3% (intermittent hoarseness not counted as complication). Local inflammation (3); interruption of electrode due to the trauma (3); chronic hoarseness and/or cough (3); generator malfunction (1); nausea, cough, and chronic neck pain (1); chronic vocal cord palsy (1)	Results suggest that chronic VNS reduces seizure frequency by at least 50% in approximately 50% of pts. Tx effect can be maintained for up to 5 yrs. *Limitations:* Retrospective study; lack of control; lack of blinding; inclusion/exclusion criteria not defined. *Quality:* Poor
Mikati et al. (2009) American University of Beirut Medical Center, Beirut, Lebanon Prospective uncontrolled study to evaluate QOL in VNS for epilepsy *F/u:* Mean 1.26 yrs (range 0.4-3.9)	n=16 consecutive pts (mean age 15.8 yrs, range 5-38; 7 males, 9 females) *Inclusion criteria:* Medically intractable epilepsy; not eligible for surgery *Exclusion criteria:* NR *Clinical hx (%pts):* Cryptogenic	After 1 to 2 wks following implantation, VNS was started and adjusted over the coming wks to 2 mA (0.25 mA/wk) at 30 Hz and 250 μsecs pulse width (stim on, 30 secs; stim off, 5 mins). *Outcome measures:* Seizure frequency, duration, and severity; mental status by IQ	QOL significantly improved in social domain (*P*=0.039) from baseline. NS differences in overall QOL, energy/fatigue, physical, emotional, cognitive, health domains, total QOL. Seizure reduction >50% was associated w/ improvement in total QOL (*P*=0.034). Mean seizure reduction from baseline (%): Age 5-18: 43.95% (0–100%) (*P*=0.026) Age 19-39: 11.25%(-175%-90%) (NS) Localized epilepsy: 52.34% (0%-100%)	Results suggest that QOL improved in the social domain, and pts who responded to VNS had improvements in overall QOL. Children, but not adults, experienced significant reductions in seizure frequency, w/ NS changes in QOL in both grps.

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
Time frame: August 2003 – November 2007 *Funding source:* NR	(62.5%) etiology; symptomatic etiology (37.5%); localization-related epilepsy (50%); generalized epilepsy (50%)	test (WAI Scale III; WISC; Denver Developmental test); QOL (ESI-55); in pediatric pts: Seizure severity and side effects (HASS; HASES); QOL (CEQ-P III; QOLCE)	(*P*=0.052; NS) Generalized epilepsy: 15.2% (–175% – 85%) (NS) NS difference between localized and generalized epilepsy regarding seizure reduction and severity, VNS current, f/u time, # of AEDs, sex, mental retardation, and age. *Complications:* NR	This was an exploratory study that was not designed to test a hypothesis. Results need to be confirmed in additional well-controlled studies. NOTE: Power to detect 50% improvement in QOL of 0.8 required sample size of 6 pts. *Limitations:* Small sample size; lack of control grp; heterogeneous pt grp; study included many subgrp comparisons, statistical validity of these comparisons is unclear; exploratory study; variable f/u time. *Quality:* Poor
Rossignol et al. (2009) Hôpital Ste-Justine, Montréal, Canada Prospective, uncontrolled study of VNS for epilepsy in very young children *F/u:* 2 yrs *Time frame:* January 2000 – December 2004 *Funding source:* NR	n=28 pts (age 2 mos – 7 yrs; 13 males, 15 females; mean medications per child, 9) *Inclusion criteria:* Pts w/ various epileptic syndromes refractory to medical tx *Exclusion criteria:* NR *Clinical hx (# pts):* Generalized idiopathic epilepsy w/ absence seizures (3); LGS (5); infantile myoclonic epilepsy of Dravet (2); myoclonic epilepsy of Doose (1); cryptogenic generalized epilepsy (5); cryptogenic bilateral partial epilepsy (7); partial symptomatic epilepsy (5); failed ketogenic diet (18); failed prior surgery (3)	Pts received VNS. Settings were adjusted wkly during 1st 6 wks of stim (from 0.25 mA to 1.5 mA), then monthly up to 6 mos, and as needed over next 18 mos. Medications were kept stable during 1st 6 mos. *Outcome measures:* Seizure frequency; neuropsychological evaluation (cognitive function, behavior, QOL); medication modifications; complications	At 2 yrs, mean seizure reduction rate was 53% per pt. >50% reduction in seizures was noted in 86% of pts w/ atonic seizures, 100% of pts w/ tonic seizures, and 75% of pts w/ myoclonic seizures. In LGS, 3/5 pts had ≥50% improvement in seizure frequency. 1 pt w/ Doose syndrome was seizure free at 2 yrs. 1 pt w/ Dravet syndrome had 90% improvement in seizure frequency, 1 pt did not respond. 8/12 pts w/ PS had ≥50% improvement, 1/12 was seizure free. Medication requirements remained the same in 8/28 (28%) pts, medication decreased in 4/28 (14%) pts, and 1 pt was free of medication. Cognitive function, behavior, and QOL were assessed at baseline and at 6 mos in 16 pts. No change in level of cognitive function. In 11/16 (69%) pts, there was improved alertness, playfulness, and global interaction.	Results suggest that VNS improved seizure frequency in some pts regardless of underlying etiology. However, there may be a difference in the proportion of responders among etiologies. Sample size of this study was too small for subgrp analyses. *Limitations:* Small sample size; lack of control grp; several different etiologies; pt selection criteria not clearly defined; instruments to assess outcomes NR in some cases. *Quality:* Poor

Authors/Study Design	Study Population	Treatment/Outcome Measures	Results/Complications	Conclusions/ Limitations/Quality Ratings
			In 26/28 pts, caregivers reported improved nighttime sleep. *Complications (# pts):* Overall, 68% of pts experienced ≥1 complication. Mild complications included throat pain, voice change, chest discomfort, local thoracic pain at site of VNS battery; dyspnea; coughing; mild dysphagia. Severe complications included discomfort at site of VNS battery necessitating surgical repositioning (2); device remove due to deep infection (2), dysphagia (1); death from upper airway obstruction unrelated to VNS (1).	

GUIDELINES

The MED Project list of medical core resources (November 2008) guided a search for health technology assessments (HTAs), systematic reviews, and clinical practice guidelines published in the previous 5 years. Additional guidelines were obtained from the Australian government's Medical Services Advisory Committee (MSAC) and National Collaborating Centre for Primary Care (NCCPC). The available reports are summarized in the following sections.

Medical Services Advisory Committee (MSAC)

In June 2008, MSAC published a health technology assessment report (MSAC, 2008). The review included evidence published from 1990 to October 2007. MSAC rated the overall body of evidence as excellent, good, satisfactory, or poor with regard to its quality, consistency, clinical impact, generalizability, and applicability. MSAC concluded that VNS is reasonably safe in the context of the condition being treated, but there is insufficient evidence of effectiveness and net benefit of VNS for patients with medically refractory epilepsy. Furthermore, MSAC recommended that public funding for VNS for epilepsy remain unchanged.

Clinical Evidence / British Medical Journal (BMJ) Publishing Group Ltd.

The report was published in 2009 and included evidence published until April 2007. The individual studies evaluated are also reviewed for this report. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to analyze the quality of the body of evidence. The report concluded that high-level VNS might reduce seizure frequency in people with partial seizures that are refractory to treatment with antiepileptic drugs. However, VNS may cause complications such as hoarseness and dyspnea, and long-term effects are unknown. The effect of different stimulation cycles is also unknown (BMJ Publishing Group, 2009).

Cochrane Organization

This report met the inclusion criteria for detailed review and is included in the evidence section (Privitera et al., 2002).

National Institute for Health and Clinical Excellence (NICE)

NICE published a guideline on VNS for epilepsy in March 2004 (NICE, 2004). A modified version of the Eccles & Mason grading scheme and hierarchy of evidence was used to grade the body of evidence (Eccles & Mason, 2001). According to NICE, VNS is 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 predominately partial seizures, with or without secondary generalized epilepsy, and generalized epilepsy.

ECONOMIC EVALUATIONS

European studies have shown VNS to be a cost-saving treatment from payer perspectives and a cost-effective treatment from a societal perspective:

- In a small sample of 20 patients, VNS improved outcomes while reducing total annual epilepsy-related medical costs by an average of $3000 per patient (Boon et al., 1999).

- VNS was found to reduce unplanned hospital costs by approximately $3000 (Ben-Menachem, Hellstrom, & Verstappen, 2002).

- Boon et al. (2002) conducted a prospective analysis of impact on ongoing costs, comparing three different treatment options for refractory epilepsy. The three treatment options were polytherapy with antiepileptic drugs, resective surgery, and VNS. Epilepsy-related direct medical costs were assessed for the 2 years preceding the treatment decision and during the follow-up interval. All groups exhibited reduction both in mean seizure frequency and in mean cost of ongoing daily treatment. Cost reduction was significantly greater in the VNS group, compared with cost reduction in the conservatively treated group. The difference in cost reduction between VNS and surgery was nonsignificant. The authors concluded that for patients in whom resective surgery is not recommended, VNS, as opposed to conservative treatment, leads to a greater reduction in epilepsy-related direct medical costs. According to their estimates, this conclusion would hold true even after accounting for the cost of VNS implantation. [NOTE: Both seizure frequency and costs were greatest to begin with in the VNS treatment group, which limits the comparability of groups.]

- Majoie et al. (2001) conducted a trial-based cost-effectiveness analysis of VNS for children with therapy-resistant Lennox-Gastaut syndrome (LGS). They concluded that VNS was a cost-effective treatment from a societal perspective. The direct healthcare costs, direct non-healthcare costs, and indirect costs were measured for 6 months prior to VNS treatment and for 6 months afterward. Total cost in all three categories declined after VNS treatment, but a statistically significant reduction was observed only for the direct healthcare costs associated with ergotherapy, for overall direct non-healthcare costs, and for the indirect cost attributed to number of days of suboptimal functioning of the child. Excluding the cost of VNS implantation, the total direct and indirect costs during the 6 months of VNS treatment were €2876 less than during the 6 preoperative months. The authors reported a payback period of 2.3 years for recouping the cost of VNS. When the cost of VNS implantation was combined with all other costs, the cost-effectiveness calculations yielded a ratio of €17 per single seizure averted. [NOTE: The study group included only 19 patients.]

No studies conducted in the United States have compared both cost and effectiveness. However, a retrospective analysis of data from a staff-model health maintenance organization (HMO) in the United States was published in 2007 (Bernstein, Barkan, & Hess, 2007). These authors analyzed total healthcare utilization by 138 patients who were implanted with VNS, comparing 1 year before with 4 years after implantation. They determined that by the fourth quarter of year 1 after implantation, the average number of outpatient visits had decreased by 12% in their study group compared with the 12-month period prior to the initiation of VNS treatment. This group difference was not statistically significant at this time point, but did reach statistical significance by the first quarter of the year 2 of the study. This measure of healthcare utilization continued to decrease throughout the duration of the study; by the end of year 4, there was a 91% decrease in outpatient visits relative to the baseline measure obtained before VNS treatment began. Other measures of healthcare utilization also exhibited similar reductions: emergency department visits decreased by 99%; hospital length of stay by 67%; and number of hospital admissions by 70%.

In 2003, Forbes published a cost-utility study from the perspective of the National Health Service in the United Kingdom (UK), incorporating capital equipment costs. In a recent letter to the editor of *Seizure*, the primary author updated the results of this study (Forbes, 2008). In 2003, the cost-utility ratio was calculated as £28,849 per quality-adjusted life year (QALY). These calculations were based on the assumption that the device's life expectancy was 5 years and that one in six patients would respond to the treatment with a greater than 50% reduction in seizure frequency. In the letter to the editor, Forbes states that technical improvements have increased the device life to at least 6 years and considers 8 years as "technically realistic." The new baseline model assumes £678 per hour of neurosurgical operating room, 1 hour of operating time per implant, £682 per day hospital costs, similar costs for explantation of infected device (2.7% explantation rate), and a 1.1% infection rate with £4774 treatment costs. Based on these new parameters, Forbes states that the new baseline estimate is £4423 per QALY gained. This value is lower with a long-life battery (£3002) and higher in a less effective device (£11,819) (NOTE: Cost data are based on UK 2006 prices.).

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APPENDIX I

MED PROJECT	Methodology Checklist: Systematic Reviews and Meta-analyses
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)	
MED Topic:	Key Question No.(s):
Checklist completed by:	Date:

Section 1: Internal validity					
In a well conducted systematic review		In this study the criterion is met:			
1.1	The study addresses an appropriate and clearly focused question.	YES	NO	UNCLEAR	N/A
1.2	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	YES	NO	UNCLEAR	N/A
1.3	***The literature search is sufficiently rigorous to identify all the relevant studies.***	YES	NO	UNCLEAR	N/A
1.4	***The criteria used to select articles for inclusion is appropriate.***	YES	NO	UNCLEAR	N/A
1.5	Study quality is assessed and taken into account.	YES	NO	UNCLEAR	N/A
1.6	There are enough similarities between the studies selected to make combining them reasonable.	YES	NO	UNCLEAR	N/A
1.7	There is a conflict of interest statement.	YES	NO	UNCLEAR	N/A
1.8	There is a description of source(s) of funding.	YES	NO	UNCLEAR	N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY					
2.1	***How well was the study done to minimize bias?*** **Code: Good, Fair or Poor**	GOOD	FAIR	POOR	
2.2	If coded as fair or poor, what is the likely direction in which bias might affect the study results?				
2.3	Are the results of this study directly applicable to the patient group targeted by this key question?	YES	NO	UNCLEAR	N/A
2.4	Other reviewer comments:				

APPENDIX II

MED PROJECT	**Methodology Checklist: Randomized Controlled Trials**				
Study identification (*Include author, title, year of publication, journal title, pages*)					
MED topic:		Key Question No(s):			
Checklist completed by:		Date:			
		Section 1: Internal validity			
In a well conducted RCT study…		In this study this criterion is:			
RANDOM ALLOCATION OF SUBJECTS					
1.1	An appropriate method of randomization was used to allocate participants to intervention groups.	YES	NO	UNCLEAR	N/A
1.2	***An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.***	YES	NO	UNCLEAR	N/A
1.3	The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES	NO	UNCLEAR	N/A
ASSESSMENT AND FOLLOW-UP					
1.4	Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	YES	NO	UNCLEAR	N/A
1.5	The intervention and control groups received the same care apart from the intervention(s) studied.	YES	NO	UNCLEAR	N/A
1.11	The study had an appropriate length of follow-up.	YES	NO	UNCLEAR	N/A
1.12	All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES	NO	UNCLEAR	N/A

1.14	What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did not complete the intervention(s)?	
1.15	*All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)*	YES NO UNCLEAR N/A

ASSESSMENT AND FOLLOW-UP, Cont.		
1.16	All relevant outcomes are measured in a standard, valid and reliable way.	YES NO UNCLEAR N/A
1.17	The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	YES NO UNCLEAR N/A
1.18	The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.19	There is a conflict of interest statement.	YES NO UNCLEAR N/A
1.20	There is a description of source(s) of funding.	YES NO UNCLEAR N/A
Section 2: Overall Study Assessment		
2.1	***How well was the study done to minimize bias?*** **Code Good, Fair, or Poor**	GOOD FAIR POOR
2.2	If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.7	Other reviewer comments:	

APPENDIX III

MED PROJECT	Methodology Checklist: Cohort Studies
Study identification (*Include author, title, year of publication, journal title, pages*)	
Review topic:	Key Question No.(s), if applicable:
Checklist completed by:	Date:

		Section 1: Internal validity			
In a well conducted cohort study:		In this study the criterion is:			
1.1	The study addresses an appropriate and clearly focused question.	YES	NO	UNCLEAR	N/A
SELECTION OF SUBJECTS					
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	YES	NO	UNCLEAR	N/A
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	YES	NO	UNCLEAR	N/A
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.	YES	NO	UNCLEAR	N/A
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?				
1.6	**Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.**	YES	NO	UNCLEAR	N/A
ASSESSMENT AND FOLLOW-UP					
1.7	The study employed a precise definition of outcome(s) appropriate to the key question(s).	YES	NO	UNCLEAR	N/A
1.8	The assessment of outcome(s) is made blind to exposure status.	YES	NO	UNCLEAR	N/A
1.9	Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	YES	NO	UNCLEAR	N/A
1.10	The measure of assessment of exposure is reliable.	YES	NO	UNCLEAR	N/A

1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	YES NO UNCLEAR N/A
1.12	Exposure level or prognostic factor is assessed more than once.	YES NO UNCLEAR N/A
1.13	The study had an appropriate length of follow-up.	YES NO UNCLEAR N/A
1.14	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	YES NO UNCLEAR N/A
CONFOUNDING		
1.15	The main potential confounders are identified and taken into account in the design and analysis.	YES NO UNCLEAR N/A
STATISTICAL ANALYSIS		
1.16	Have confidence intervals been provided?	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.17	There is a conflict of interest statement.	YES NO UNCLEAR N/A
1.18	There is a description of source(s) of funding.	YES NO UNCLEAR N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code Good, Fair, or Poor*	GOOD FAIR POOR
2.2	If coded as Fair, or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.4	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	YES NO UNCLEAR N/A
2.5	Other reviewer comments:	

Health Technology Assessment

HTA Final Report
Vagus Nerve Stimulation for Depression

Date: Friday, July 31st, 2009

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Vagus Nerve Stimulation for Depression

Provided by:

MEDICAID EVIDENCE-BASED DECISIONS PROJECT (MED)

This report was written by Hayes Inc. on behalf of the Center for Evidence-based Policy at Oregon Health & Science University (the Center). The Center is a policy resource and is not providing any legal or business advice. This Report is intended for the benefit of the Medicaid Evidence-based Decisions Project participant organizations and their constituent decision-making bodies. This report is not a Policy Statement of the Center for Evidence-based Policy.

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VAGUS NERVE STIMULATION FOR DEPRESSION

PURPOSE OF THE TECHNOLOGY

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.

EXECUTIVE SUMMARY

Clinical Overview

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.

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.

Policy Context

Vagus nerve stimulation (VNS) is a topic of interest to members of the Oregon Health & Science University Medicaid Evidence-based Decision (OHSU MED) collaboration and the Washington State Health Care Authority (HSA). Accordingly, VNS for depression is one of seven health technologies selected by the Oregon health and Science University MED Project and by the Washington State Health Care Authority (HCA) for review in 2009 (HCA, 2008). VNS has been proposed as an adjunct to medical treatment for the treatment of chronic, medically refractory, major depression but issues remain regarding its efficacy and safety.

Scope

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, 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.

Methods

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 (see **Appendix IV**), although, to date, complete data sets have not been published for all of the studies.

The search of the peer-reviewed medical literature yielded several articles reporting on:

- One randomized controlled clinical trial (D02)
- One nonrandomized comparison of the D02 results with standard treatment (D04 study)
- One post hoc nonrandomized comparative study of VNS for bipolar versus unipolar depression
- One small, nonrandomized controlled study
- Five prospective, open-label, uncontrolled studies including three studies of the D-series of Cyberonics trials (D01; D03; D06).

The studies enrolled 9 to 235 adult patients with chronic, severe, treatment-resistant major depression disorder (MDD) or bipolar disorder. These studies performed VNS using the NeuroCybernetic Prosthesis (NCP) System (Cyberonics), also referred to as the VNS Therapy System. In the randomized controlled D02 trial, patients were randomly assigned to receive active VNS or sham VNS following the 2-week recovery period. At the end of the acute phase, the study was unblinded and the patients in the sham group who were still depressed were offered active VNS.

In general, the primary outcome measure was a ≥ 50% improvement in the Hamilton Depression Rating Scale ($HDRS_{28}$ or $HDRS_{24}$) scores versus baseline; patients who achieved this level of improvement were referred to as responders. For the 2-year analysis of the D01 and D02 studies, this threshold was lowered to 40% improvement. Patients who achieved an $HDRS_{28}$ score of 10 or less were considered to be in remission. Secondary outcome measures included improvement in HDRS scores, the 30-Item Inventory of Depressive Symptomatology-Self-Report ($IDS\text{-}SR_{30}$), Montgomery-Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Clinical Global Impressions-Improvement (CGI-I) scale, and Clinical Global Impressions-Severity (CGI-S) scale. Functional outcomes were assessed using the Medical Outcomes Study 36-item Short Form (MOS SF-36) and the Global Assessment

of Function (GAF). In addition, some studies presented the incidence and length of hospitalization, the number of psychotherapy treatments, and changes in medication use. Long-term studies also evaluated the percentage of patients maintaining the response for 12 to 24 months of VNS. Complications were also reported.

The quality of selected primary studies was assessed with the aid of MED checklists for RCTs and cohort studies and was graded as "good," "fair," or "poor." Overall bodies of evidence by outcome and indication were graded as "high," "moderate," or "low" quality according to the GRADE system.

Findings

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 shared many 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 $HDRS_{28}$, 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 ≥ 50% improvements in $HDRS_{24}$ 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 $HDRS_{24}$ 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 ≥ 40% rather than ≥ 50% in $HDRS_{24}$ scores. Therefore, if the original threshold were used to evaluate the data, the rate for maintaining the treatment benefit would likely be lower.

The combined evidence is low quality and does not support the conclusion that that VNS therapy reduces depression or improves quality of life in patients with chronic, severe, treatment-resistant MDD or bipolar disorders. The single RCT showed no statistical improvement in the main study outcomes suggesting a need for additional RCTs.

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. Some complications 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.

3. Does effectiveness vary by age, response to antidepressants, or other patient characteristics?

The evidence is insufficient to establish patient selection criteria for VNS in patients with treatment-resistant depression, and significant predictors of response have not yet been identified.

Conclusions and Discussion

The currently available evidence is of low overall quality and does not support the use of VNS as an adjunct therapy in adult patients with treatment-resistant MDD and bipolar disorders. While a moderate treatment effect was observed in the uncontrolled studies, the only randomized controlled study failed to demonstrate a statistically significant difference in primary outcomes after 10 weeks of active or sham VNS. There is no evidence from good-quality controlled studies investigating the long-term effectiveness of VNS in the treatment of depression. For participants in uncontrolled studies lasting up to 24 months, VNS improved depression and maintained the treatment benefit in a large number. There is a placebo effect associated with depression treatments (Brunoni et al., 2009). Therefore, the lack of data from prospective, randomized, controlled clinical studies considerably limits the conclusions that can be drawn from the available evidence. In patients with severe, treatment-resistant depression, a ≥ 50% improvement of HDRS baseline scores is generally considered clinically significant. However, patients with high baseline HDRS scores could still have moderate to severe depression, even after 50% improvement in scores. Furthermore, although most complications are mild, VNS can cause severe complications. Changing the stimulation parameters reverses many minor complications such as voice changes while others are permanent or may require device explantation. One important concern is that VNS may increase

depression and suicide ideation and suicide attempts, although in one nonrandomized, controlled study there was no difference in these rates between VNS and standard treatment. As VNS may cause serious complications, it is necessary to know who is at risk for serious complications and for which patients the potential benefits clearly outweigh these risks. There are currently two studies in progress that may provide additional data in the evaluation of VNS for depression (ClinicalTrials.gov, 2009a, 2009b). One is a patient registry study, aimed at providing long-term safety and effectiveness data; and one is a randomized study comparing different stimulation settings. The latter study will be completed in 2010, and this review should be updated when the results are published, as they may impact the conclusions of this report.

In clinical practice, patients with chronic, severe, medication-resistant depression have limited treatment options. The FDA has approved VNS for patients with chronic, severe MDD and bipolar disorders, and, therefore, this treatment is available in a clinical setting. However, clinicians who choose VNS as a treatment option have to know that the effectiveness and safety is not proven. The results from controlled studies were conflicting, and in the uncontrolled trials relatively few patients responded with a clinically significant improvement in depression severity; very few patients achieved remission, and it is not clear whether this outcome was related to VNS in clinical trials. The potentially severe complications of this treatment require that the patient be closely monitored and treatment be stopped if treatment-related complications occur that do not resolve with a change in stimulation parameters. Another factor complicating this treatment is the difficulty in titrating the VNS stimulation parameters to achieve a positive treatment response. The treatment effect is delayed in VNS for epilepsy, and this may also be the case in VNS for depression; therefore, it is difficult to decide when to change stimulation settings and whether deciding on the highest tolerable stimulation parameters equals a positive treatment response. Data from a randomized study comparing different stimulation settings that may guide treatment will be available in 2010 (ClinicalTrials.gov, 2009a).

BACKGROUND

Clinical Overview

Depression is a mood disorder that affects approximately 5% to 10% of adults in the United States. 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. The most common types of depression include:

- Major depression
- Dysthymia
- Bipolar disorder

Major depression disorder (MDD) is characterized by a combination of symptoms occurring during a major depressive episode (MDE) (see list below) that interfere with the person's daily activities, such as their ability to work, sleep, and eat. An MDE may occur several times in a lifetime and may last for several weeks or years. Dysthymia is a less severe type of depression, which involves long-term chronic symptoms that are not disabling but prevent the patient from feeling good. Bipolar disorder, also referred to as manic-depressive disorder, is characterized by drastic mood changes—a severe high (mania, manic cycle) followed by a low (depression, depressed cycle). This health technology assessment focuses on the treatment of MDD and bipolar disorder.

According to a review of several cross-national surveys, the lifetime rates of MDD ranged from 3.9% (Japan) to 16.9% (U.S.), and the lifetime rates of bipolar disorders ranged from 0.3% to 1.5%, respectively (Weissman & Gameroff, 2003). Women experience depression approximately twice as often as men. The diagnosis is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Clinical history is evaluated and physical examination is performed to identify other factors that may cause or contribute to the disorder, such as substance abuse and neurological disorders (NIMH, 2009).

The number and severity of symptoms vary among patients. Symptoms of depression experienced during a depressive episode may include the following (Andrade et al., 2003; NIMH, 2009; Weissman, 2003):

- Sad or anxious mood
- Persistent feelings of hopelessness, pessimism, guilt, worthlessness, or helplessness
- Loss of interest or enjoyment of formerly pleasurable activities (e.g., hobbies, sex)
- Fatigue or decreased physical, mental, and emotional energy
- Difficulties remembering, concentrating, or making decisions
- Loss of appetite and weight loss or overeating and weight gain

- Suicidal thoughts or suicide attempt
- Restlessness or irritability
- Persistent physical symptoms that do not respond to treatment (e.g., headache, chronic pain)

Symptoms of mania characteristic for bipolar disorder may include:

- Abnormal or excessive elation
- Abnormal or excessive irritability
- Racing thoughts
- Overly talkative
- Increased sexual desire
- Inappropriate social behavior
- Grandiose notions
- Poor judgment
- Noticeably increased energy
- Decreased need for sleep

Treatments for Depression

Psychotherapy and Pharmacotherapy: 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. Patients generally begin to experience symptom improvement after 4 to 8 weeks on medication. In most cases, the patients will stay on the medication for 6 to 12 months to allow the medication to reach full effectiveness and to prevent a relapse. Early antidepressants, developed in the 1960s to 1980s, included tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Today, TCAs (imipramine, amitriptyline, nortriptyline, desipramine) and MAOIs (phenelzine, tranylcypromine, isocaroboxazid) are used as a second or third line of treatment. These medications primarily affect two neurotransmitters, norepinephrine and serotonin. While effective for the treatment of depression, these early treatments were associated with significant side effects such as dry mouth, constipation, urinary problems, sexual side effects, blurred vision, dizziness, drowsiness, and increased heart rate. In addition, patients taking MAOIs need to avoid certain foods that contain high levels of tyramine (e.g., cheese, wine, pickles), as the interaction of tyramine with MAOIs can cause a sudden increase in blood pressure leading to stroke. In the 1990s, a new generation of antidepressant, selective serotonin-reuptake inhibitors (SSRIs), was introduced. SSRIs primarily affect only one neurotransmitter, serotonin. Examples of SSRIs include fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram. Other new-generation drugs, which affect norepinephrine and serotonin, include dopamine-norepinephrine reuptake inhibitors (bupropion), serotonin-norepinephrine reuptake inhibitors (venlafaxine), serotonin modulators (nefazodone, trazodone), and norepinephrine-serotonin modulators (mirtazapine). These new antidepressants have different side effects, including sexual problems (reversible), headache, nausea, nervousness and

insomnia, and agitation. Alcohol and other drugs may interact with these antidepressant medications (FDA, 2009b; NIMH, 2009).

Lithium carbonate is a common treatment for bipolar disorder. It is presumed to affect neurotransmitter regulation, but the precise mechanism of action is unknown. Side effects include thirst, reduction in thyroid function, weight gain, and a fine tremor in the hands. Lithium can also affect kidney function. Lithium is used as monotherapy or is combined with an antidepressant for the first-line treatment of bipolar depression. Another choice of first-line treatment of the depressive episode is lamotrigine. Lithium or valproate plus an antipsychotic are current first-line treatments of manic or mixed episodes. SSRIs, MAOIs, or venlafaxine are common second-line treatments (APA, 2002).

Electroconvulsive Therapy (ECT): ECT is an alternative treatment for severe and life-threatening depression or for patients who cannot take or do not respond to antidepressant medication. It may be used in combination with antidepressants. During ECT, the patient receives a muscle relaxant, and electrodes are placed at specific locations on the head to deliver electrical impulses. Stimulation is carried out 3 times per week for up to 5 weeks. ECT relieves symptoms in 50% to 80% of cases. Patients may experience transient heart rhythm disturbances following ECT. Short-term memory loss is the most common side effect, but it usually subsides within 7 months of treatment. Approximately 20% to 50% of patients experience recurrence of depression within 6 months of treatment. To prevent recurrence, patients may receive antidepressant medication and/or additional ECT to maintain the treatment effect (Bolwig, 2003; NIMH, 2009).

Vagus Nerve Stimulation (VNS): VNS has been introduced as an adjunct to antidepressant treatment in patients with MDD or bipolar disorder. The vagus nerve is the tenth and longest cranial nerve. Its name is derived from the Latin meaning “wandering” due to its complex path through the body from the brain stem through organs in the neck, thorax, and abdomen. The vagus nerve innervates vital structures in the body, such as the heart, intestines, esophagus, stomach, liver, and muscles of vocalization. In the brain, the vagus nerve forms connections with the medulla; most connections are to the nucleus tractus solaritus (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. It is also capable of processing extensive information.

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. Clinical studies of VNS were successful in reducing seizure frequencies and resulted in the 1997 approval by the Food and Drug Administration (FDA) of the neurocybernetic prosthesis, an implantable generator that provides intermittent electrical stimulation to the cervical portion of the vagus nerve. During these clinical trials, the investigators observed improved mood and cognition in epilepsy patients who received VNS. In addition, other observations indicate that VNS may be effective for the treatment of depression, including:

- 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 reduces 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; Follesa 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).

Policy Context

Vagus nerve stimulation (VNS) for depression is a topic of interest to members of the Oregon Health & Science University Medicaid Evidence-based Decision (OHSU MED) collaboration and the Washington State Health Care Authority (HSA). Accordingly, VNS for depression is one of seven health technologies selected by the Oregon health and Science University MED Project and by the Washington State Health Care Authority (HCA) for review in 2009 (HCA, 2008). VNS has been proposed as an adjunct to medical treatment for the treatment of chronic, medically refractory, major depression. The VNS system consists of an implantable pulse generator and lead and an external programming system used to change stimulation settings. Given the potential benefits of VNS, healthcare decision makers will benefit from a systematic reappraisal of the evidence. This rapid review evaluates primary evidence of VNS for patients with chronic, severe major depression and bipolar disorders.

In July 2005, the Food and Drug Administration (FDA) approved the NeuroCybernetic Prosthesis (NCP)® System, also called the VNS Therapy™ 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). There has been controversy regarding this decision based on concerns that there was insufficient evidence supporting the claim that VNS improves depression and is safe for patients with major depression or bipolar disorder.

In 2007, the Centers for Medicare & Medicaid Services (CMS) responded to a request from Cyberonics Inc. to reconsider coverage for VNS for depression. However, the review of the evidence resulted in a noncoverage decision, and CMS does not cover VNS as a treatment for chronic major depression at this time (CMS, 2009).

Scope

- Population(s): Patients with chronic, severe treatment-resistant MDD or bipolar disorder.
- Intervention(s): VNS as an adjunct to medical treatment.
- Comparator(s): Pharmacotherapy, psychotherapy, electroconvulsive therapy.
- Outcome(s): Changes in depression severity, complications, quality of life, function, length of depression-related hospitalization, number of required psychiatric treatments.

This rapid review addresses the following key questions:

- *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 quality of life?*
- *Are vagus nerve stimulators safe?*
- *Does effectiveness vary by age, response to antidepressants, or other patient characteristics?*

TECHNOLOGY DESCRIPTION

The only device currently approved by the Food and Drug Administration (FDA) for vagus nerve stimulation (VNS), the NeuroCybernetic Prosthesis (NCP)® System, also marketed as the VNS Therapy™ System (Cyberonics Inc.), consists of a programmable generator that is implanted subcutaneously in the chest and delivers pulses of current via electrodes attached to the vagus nerve in the left side of the neck. The stimulus is delivered periodically as a charge-balanced, biphasic, constant current pulse. The stimulation settings are tailored to individual patient tolerance; the most commonly studied stimulation paradigm has been a 20- to 30-Hz, 1.0- to 2.0-mA, 500-microsecond (msec) pulse width with 30 seconds on and 5 minutes off, 24 hours per day. Safety features prevent sudden or excessive bursts of current. The intensity, width, and frequency of the electrical pulse can be adjusted, and telemetry data regarding the operating characteristics of the pulse generator can be retrieved with a programming wand using software run on a personal computer. Patients also have control of the stimulator by means of a magnet (Models 220-3 and 220-4 VNS Therapy Magnets), which can be worn on the wrist like a bracelet or watch, or clipped to a belt or pants. If there is discomfort or if the device is malfunctioning, stimulation can be stopped by placing the magnet over the vagus nerve stimulator. The stimulator will resume as soon as the magnet is removed (Cyberonics, 2007). Microwaves or airport security systems do not affect the device; however, strong electromagnetic fields may cause the device to activate. Implantation of the NCP System takes approximately 1 hour and can be performed under general or local anesthesia (Reid, 1990; Schachter & Saper, 1998; Terry, Tarver, & Zabara, 1990). The VNS Therapy System includes a handheld computer, programming software, and a programming wand; these components are used to interrogate the pulse generator and modify stored simulation parameters (Cyberonics, 2007).

Washington State Data

Data from two Washington State Agencies were provided by the Health Technology Assessment Program. HTA coordinates the collection of any relevant agency utilization data.

Vagus Nerve Stimulation (VNS) is a selected topic. VNS uses a stimulator that sends electric impulses to the left vagus nerve in the neck via a lead implanted under the skin. VNS affects blood flow to different parts of the brain and affect neurotransmitters. VNS implantation is usually done as an outpatient procedure.

Estimates for costs and utilization from the Uniform Medical Plan and Washington State's Medicaid program are presented below in Table A. They provide an estimate of base costs and may not include all costs for Vagal Nerve Stimulation procedures and treatments. Information on relevant procedure and diagnostic codes is included after the result tables.

Table A:

Total* Payments for Vagus Nerve Stimulators

UMP & Medicaid Only | 2003-2008

	2003	2004	2005	2006	2007	2008	Total
Epilepsy	$74,053	$312,322	$276,473	$371,855	$510,892	$407,164	**$1,952,758**
Depression	$12,514	$0	$0	$7,426	$1,020	$1,240	**$22,200**
Total	$86,567	$312,322	$276,473	$379,281	$511,912	$408,404	**$1,974,958**

* Total includes inpatient, outpatient, implantations, revisions, removals, analysis, and medical devices. Total does not include physician services for assessment and maintenance and other costs that are not identifiable specific to the device.

Implantation Procedures by Condition

UMP & Medicaid Only | 2003-2008

Condition	Total
Epilepsy (345.41, 345.51, 780.39)	82
Epilepsy (345.xx, excluding above)	52
Depression (296.xx, 311)	4
Total	**138**

Implantation Procedures

UMP & Medicaid Only | 2003 - 2008

Procedure Code	Total
64553 (percutaneous implantation of neuroelectrodes)	2
64573 (incision for implantation of neuroelectrodes – cranial nerve)	136
Total	**138**

Procedure Codes

ICD9 Operation Codes
04.92 – Implantation or replacement of peripheral neurostimulator lead(s)
04.93 – Removal of peripheral neurostimulator lead(s) (coded with 86.05)
86.94 – Insertion or replacement of single array neurostimulator pulse generator, not specified as rechargeable
86.95 – Insertion or replacement of dual array neurostimulator pulse generator, not specified as rechargeable
86.96 – Insertion or replacement of other neurostimulator pulse generator
86.97 – Insertion or replacement of single array rechargeable neurostimulator pulse generator
86.98 – Insertion or replacement of dual array rechargeable neurostimulator pulse generator

CPT Codes
61885 – Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886 – Two or more arrays
61888 – Revision or removal of cranial neurostimulator pulse generator or receiver
64553 – Percutaneous implantation of neurostimulator electrodes; cranial nerve
64573 – Incision for implantation of neurostimulator electrodes; cranial nerve
95970 – Electronic analysis of implanted neurostimulator pulse generator system; simple or complex brain, spinal cord, or peripheral neurostimulator pulse generator/transmitter, without reprogramming
95974 – Complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour
95975 – Each additional 30 minutes

HCPCS Codes
C1767, 1778
L8680, L8681, L8682, L8683, L8685, L8686, L8687, L8688, and L8689

ICD-9 Diagnosis Codes
ICD-9-CM Diagnosis 345.11
Generalized convulsive epilepsy with intractable epilepsy

ICD-9-CM Diagnosis 345.41
Partial epilepsy with intractable epilepsy

ICD-9-CM Diagnosis 345.51
Partial epilepsy without impairment of consciousness with intractable epilepsy

ICD-9-CM Diagnosis 345.61
Infantile spasms with intractable epilepsy

ICD-9-CM Diagnosis 345.71
Epilepsia partialis continua with intractable epilepsy

ICD-9-CM Diagnosis 345.81
Other forms of epilepsy with intractable epilepsy

ICD-9-CM Diagnosis 345.91
Epilepsy unspecified with intractable epilepsy

ICD-9-CM Diagnosis 780.39
Other convulsions

METHODS

Search Strategy and Study Selection Criteria

Evidence for this report was obtained from a computerized search of the peer-reviewed medical literature using the MEDLINE, EMBASE, and Cochrane Review databases, spanning 1997 to June 2009. Search terms included *bipolar disorder*, *depression*, *major depression*, *dysthymia*, or *obsessive-compulsive disorder*, combined with *vagus nerve stimulation*, *vagal nerve stimulation*, *VNS*, or *electrical stimulation*. The search was restricted to clinical trials in humans and to English-language publications.

Inclusion Criteria: This rapid review selected peer-reviewed medical articles meeting the following criteria:

- Population(s): Patients with chronic, severe, treatment-resistant MDD or bipolar disorder.
- Intervention(s): VNS as an adjunct to medical treatment.
- Comparator(s): Pharmacotherapy, psychotherapy, electroconvulsive therapy.
- Outcome(s): Changes in depression severity, complications, quality of life, function, length of depression-related hospitalization, number of required psychiatric treatments.

Additional selection criteria included: (1) meta-analyses; (2) randomized controlled clinical trials and uncontrolled studies in humans evaluating vagus nerve stimulation (VNS) in adult patients with treatment-resistant major depression or bipolar disorder and published in English; (3) clinical trials evaluating at least one clinically important outcome measure, including changes in symptoms of depression, function, quality of life, and complications; and (4) clinical trials investigating other clinically relevant outcomes such as hospital length of stay, the number of psychotherapy treatments required by patients, and changes in psychotropic medication use.

Exclusion Criteria: Narrative reviews that did not evaluate, summarize, and analyze primary evidence were excluded from this detailed review. In addition, primary evidence consisting of case reports, preclinical studies, studies in animals, and studies measuring the affect of VNS on brain function and levels of brain chemicals were also excluded. Meta-analyses published in or before 2003 were also excluded.

Selected Reviews and Studies

The search did not identify a meta-analysis meeting 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); data from a number of these studies were presented to the FDA to support the Premarket Approval (PMA) application. Overall, the manufacturer planned and/or executed six studies, designated D01 to D06 (see **Appendix IV**), 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 of VNS for treatment-resistant depression (D02 trial) (Carpenter et al., 2004; Rush, Marangell et al., 2005); data from this trial were used in these controlled trials.
  - One post hoc comparative analysis of patients with bipolar disorder versus patients with unipolar depression who had participated in the D02 trial (Nierenberg, Alpert, Gardner-Schuster, Seay, & Mischoulon, 2008).
  - One nonrandomized comparison study comparing data from the D02 trial with data from another study evaluating standard therapy for treatment-resistant depression (D04 trial) (George et al., 2005).
- One small, prospective, open-label study using sex-matched and age-matched controls evaluated VNS for major depression disorder (Sperling, Reulbach, & Kornhuber, 2009).

The remaining evidence was from five uncontrolled studies, reported by numerous articles. There were two articles reporting on the prospective, uncontrolled extension of the RCT (Rush, Sackeim et al., 2005; Sackeim et al., 2007). There were six articles reporting data from one open-label, nonrandomized, uncontrolled clinical study (D01 trial) (Marangell et al., 2002; Nahas et al., 2005; Rush et al., 2000; Sackeim et al., 2007; Sackeim, Keilp et al., 2001; Sackeim, Rush et al., 2001). In addition, one study reported on the results of a prospective, open-label, single-arm study—the D03 trial (Schlaepfer et al., 2008). Finally, the evidence also included one small, prospective, open-label, single-arm pilot study of VNS for chronic treatment-resistant depression (Corcoran, Thomas, Phillips, & O'Keane, 2006); and one prospective, open-label, single-arm study investigating VNS in patients with rapid cycling bipolar disorder (possibly D06 study; Marangell et al., 2008). Please consult the evidence table for specific quality ratings.

Quality Assessment

Systematic Reviews: The quality of selected *systematic reviews* was evaluated with the MED Project checklist for systematic reviews (**Appendix I**).

Primary Studies: Individual primary studies were first rated based on study design:

- Good = randomized controlled trials (RCTs).
- Fair = quasi-RCT, nonrandomized controlled study, or nonrandomized comparative study).
- Poor = studies without concurrent control or comparison groups.

The quality ratings for studies were then modified based on study strengths and limitations, using the MED Project checklists for RCTs (**Appendix II**) and cohort studies (**Appendix III**). For uncontrolled/noncomparison studies, no formal checklist was used. However, quality factors were detailed in the evidence tables and could potentially upgrade an uncontrolled study to a higher quality rating.

Body of Evidence Evaluation: For each clinically significant outcome, e.g., healing or functional status, the overall quality of the body of evidence was evaluated according to the GRADE guidelines (Atkins et al., 2004; Guyatt et al., 2008). The following categories were observed:

- High = further research is very unlikely to change our confidence in the estimate of effect.
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, or no estimate of effect can be made at this time.

In the GRADE system, evidence based on RCTs is considered to be the highest quality evidence. However, a high quality rating can be downgraded on the basis of the methodological limitations of individual studies and other factors, such as inconsistency across studies. Evidence from study designs not usually considered high quality, i.e., nonrandomized controlled or comparative studies and uncontrolled studies, can sometimes be upgraded.

Other Considerations: When the quality of the evidence has been graded for each outcome, several additional considerations are important before recommendations can be made. These considerations include the relative importance of the various outcomes, the magnitude (clinical significance) of observed benefits, the benefits of the technology weighed against observed and potential harms, the availability and effectiveness of alternatives, and patient compliance issues. Such issues will be reviewed in the overall conclusion of this rapid review.

FINDINGS

The studies enrolled 9 to 235 adult patients with chronic, severe, treatment-resistant major depression disorder (MDD) or bipolar disorder. These studies performed VNS using the NeuroCybernetic Prosthesis (NCP) System (Cyberonics, 2007), also referred to as the VNS Therapy System. Device implantation was performed under general or local anesthesia, and the programmable generator was implanted subcutaneously in the chest, where it delivered pulses of current via electrodes attached to the vagus nerve in the left side of the neck. VNS was activated after a 2-week recovery period following surgery. In the subsequent 2 weeks, the stimulation parameters were adjusted for each patient individually to the maximum level comfortable to the patient. In the D01 study, outcomes were assessed at 12 weeks and 12 months following surgery; Nahas et al. (2005) and Sackeim, Brannan, Rush, George, Marangell, & Allen (2007) reported on the 12- and 24-month outcomes from an open-label, single-arm extension of the D01 trial. In the randomized controlled D02 trial, patients were randomly assigned to receive active VNS or sham VNS following the 2-week recovery period. At the end of the acute phase, the study was unblinded and patients in the sham group who were still depressed were offered active VNS. The open-label phase of the D02 trial was continued for 24 months (Sackeim et al., 2007). The prospective, open-label, single-arm D03 study provided data for up to 12 months of VNS (Schlaepfer et al., 2008). The treatment time was 12 months for the three studies that did not belong to the D01 to D04 series (Corcoran et al., 2006; Marangell et al., 2008; Sperling et al., 2009).

In the D01 to D04 studies, the primary outcome measure was a ≥ 50% improvement in the Hamilton Depression Rating Scale (D01, $HDRS_{28}$; D02 and D03, $HDRS_{24}$) scores versus baseline; patients who achieved this level of improvement were referred to as responders. For the 2-year analysis of the D01 and D02 studies, this threshold was lowered to 40% improvement (Sackeim et al., 2007). Patients who achieved an $HDRS_{28}$ score of 10 or less were considered to be in remission. Secondary outcome measures included improvement in the 30-item Inventory of Depressive Symptomatology-Self-Report ($IDS\text{-}SR_{30}$), Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979), Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978), Clinical Global Impressions-Improvement (CGI-I) scale and Clinical Global Impressions-Severity (CGI-S) scale (Guy, 1976), and the Global Assessment of Function (GAF) (APA, 1994). Functional outcomes were assessed using the Medical Outcomes Study 36-item Short Form (MOS SF-36) (Ware & Sherbourne, 1992). In addition, some studies presented the incidence and length of hospitalization, the number of psychotherapy treatments, and changes in medication use. Long-term studies also evaluated the percentage of patients maintaining the response for 12 to 24 months of VNS. In the D01 study, neurocognitive testing was performed in 27 of 60 patients (Sackeim, Keilp et al., 2001). The primary objective of the addendum study to the D02 clinical trial was to evaluate the effect of VNS on concentrations of various cerebral spinal fluid analytes (homovanillic acid, gamma-aminobutyric acid, norepinephrine, 5-hydroxyindoleacetic acid, 3-methoxy-4-

hydroxyphenylglycol) (Carpenter et al., 2004). Type and rate of complications were also reported.

Changes in depression cannot be measured directly and, therefore, rely on standardized instruments such as the HDRS. Irrespective of the type of instrument that is used, there are several ways in which these changes can be documented:

- Absolute changes in depression scores versus baseline and/or versus a control group.
- Relative changes expressed as a percentage of change versus baseline values.
- Percentage of patients reaching scores that reach a clinically meaningful threshold, e.g., signifying remission or a lower level of depression.
- Percentage of patients achieving a ≥ 50% reduction in depression scores.

From a clinical perspective, it is important to determine whether changes in these scores are meaningful to the patient. In patients with severe treatment-resistant depression, a ≥ 50% improvement of HDRS baseline scores is generally considered clinically significant. However, patients with high scores could still have moderate to severe depression, even after ≥ 50% improvement in scores. Therefore, it is always important to also look at the patient's final depression scores to determine whether the patient has truly improved, showing residual mild or moderate depression, or whether, despite a 50% improvement, the patient still suffers from severe depression.

Differences in the absolute scores versus baseline and between the active treatment and the control may be statistically significant but are also not necessarily clinically relevant because, despite a statistically significant improvement, the patient may still suffer from severe depression. Therefore, the final depression has to be evaluated and be brought into a clinical context. Certain thresholds can be used to define a clinically meaningful outcome. The clinical studies evaluated in this review used a HDRS score of 10 as a threshold for remission. Other thresholds were not used, although theoretically these could be meaningful; for example, a threshold could differentiate severe from moderate and mild depression. Patients that reach a level below this threshold can be considered responders even if they were not in remission.

Overall, depression can be assessed with a variety of instruments. Regardless of the method used to demonstrate effectiveness of the treatment, the final depression score has to be taken into account when evaluating the overall results. Relying on statistically significant relative or absolute changes can be misleading if the final depression scores does not fall below the threshold for severe depression.

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 quality of life?

EVIDENCE FOR MAJOR DEPRESSION AND BIPOLAR DISORDER I AND II

Results of the Randomized Controlled Trials:

The search of the peer-reviewed medical literature identified one randomized controlled trial (RCT). Rush, Marangell et al. (2005) reported outcomes of a 12-week RCT, referred to in the FDA summary of safety and effectiveness data documentation as the D02 acute study (FDA, 2005b). In this double-blind RCT, active VNS with an implantable device (n=112) was compared with sham VNS (n=110) with an identical device that was not turned on. Active VNS was no more effective that 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) with multiple regimens of standard treatments. Eligible patients (mean age, 46.5 years) had baseline Hamilton Depression Rating Scale (HDRS) scores $\geq$ 20 (mean baseline score, 29.2) and were in an MDE (median duration, 33.5 months) that was unresponsive to at least two courses of treatment with different classes of antidepressant medications, and at least 6 weeks of psychotherapy. In addition, approximately 36% of the study population had undergone electroconvulsive therapy (ECT) during the current MDE. The primary outcome measure of VNS efficacy, defined as a response, was $\geq$ 50% reduction from baseline on the HDRS after 10 weeks of active or sham therapy. Secondary outcome measures included the Montgomery-Åsberg Depression Rating Scale (MADRS), the Inventory of Depressive Symptomatology-Self-Report (IDS-SR), the Young Mania Rating Scale (YMRS), Clinical Global Impressions-Improvement (CGI-I) and -Severity (CGI-S) indices, and the Medical Outcomes Study 36-item short form (MOS SF-36). Patients were evaluated prior to implantation and weekly thereafter, including a 2-week "recovery" period postimplantation during which no active stimulation was provided. Concomitant therapy with up to five different medications was permitted if patients were maintained on a stable regimen throughout the study. Active and sham treatment groups were well balanced with respect to baseline characteristics. 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.

Carpenter et al. (2004) evaluated the metabolic effects of VNS in patients enrolled in the D02 trial. At 12 weeks following surgery, homovanillic acid concentrations were significantly different between the two treatment arms, with an increase of 18.8% in the active VNS group and a reduction of 9.4% in the sham VNS group (*P*=0.03). Mean gamma-aminobutyric acid, norepinephrine, 5-hydroxyindoleacetic acid, and 3-methoxy-4-hydroxyphenylglycol concentrations were not significantly different. These results indicate that VNS may increase cerebrospinal fluid homovanillic acid concentrations, which is suggestive of an effect on central nervous system (CNS) metabolism and, thus, function. However, this effect was not reflected in the clinical outcomes; patients in the sham-VNS and active-VNS groups experienced similar changes in HDRS, CGI-S, and CGI-I, with no statistically significant intergroup differences. Small study size limited the

quality of the evidence. Only 21 of 235 patients elected to participate in this study, an addendum to the original D02; therefore, sample size may have been too small to detect a treatment effect.

Results from Nonrandomized Controlled Studies:

Rush, Sackeim et al. (2005) reported outcomes of the 12-month open-label extension trial, referred to in the FDA summary of safety and effectiveness data documentation as the D02 long-term phase (FDA, 2005b). These long-term findings were then compared with 12-month results of another trial being sponsored by the manufacturer at several centers that were also participating in the pivotal investigation (George et al., 2005). This unrelated observational study is referred to in the FDA summary of safety and effectiveness data documentation as D04 (FDA, 2005b). It is important to note that this trial reports on the same VNS population as the D02 trial; no new VNS data were gathered.

George et al. (2005) 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. This combined analysis is referred to in the FDA summary of safety and effectiveness data documentation as the pivotal D02/D04 comparison study (FDA, 2005b). 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 Hamilton Depression Rating Scale (HDRS) over 12 months. For the entire study sample, 27% of VNS+TAU patients showed a ≥ 50% improvement in HDRS scores compared with 15% of TAU patients (P=0.011). However, there were 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 shared many similar baseline characteristics; there were significant differences between the two groups in severity and history of depression, race, and use of certain concomitant therapies. In addition, usual care was not standardized across all participating study sites, and VNS patients received concomitant therapies that may have confounded interpretation of findings. 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 achieved a ≥ 50% improvement in HDRS score (P=0.27) (FDA, 2005b).

In a small, prospective, nonrandomized, controlled study, Sperling, Reulbach, & Kornhuber (2009) measured improvement in depression ($HDRS_{28}$) for 12 months. Changes in the duration of depression-related hospitalization and the number of psychiatric treatments per year were also evaluated. The study enrolled nine patients

receiving VNS as an adjunct to pharmacotherapy and psychotherapy and nine patients, sex-matched and age-matched to the VNS group, who continued pharmacotherapy and psychotherapy but did not undergo device implantation. VNS significantly improved $HDRS_{28}$ scores from 23.7 to 10.2 points at 12 months (P<0.001). There was no significant change in the control group. VNS also significantly decreased the yearly number of days hospitalized from 65 to 44, while the hospitalization rate in the control group did not change. VNS also reduced the number of psychiatric treatments from 33 to 24 per year. There was no statistically significant change in this parameter for the control group. The respective values for the control group were 24.9 and 25.3 treatments per year. While the study results suggest that VNS may improve depression, the study used only one instrument to assess this outcome and did not include a sham control; therefore, the result must be interpreted with caution since a placebo effect may have confounded the results. However, the additional outcomes, duration of hospitalization, and number of psychiatric treatments are indirect measures suggesting that VNS may improve depression severity. Nevertheless, the small sample size and lack of blinded assessment are additional factors compromising the quality of the evidence (Sperling et al., 2009).

Results from Uncontrolled Studies (prospective, open-label, uncontrolled extension study of the RCT):

Rush, Sackeim et al. (2005) reported outcomes of the 12-month open-label extension trial, referred to in the FDA summary of safety and effectiveness data documentation as the D02 long-term phase (FDA, 2005b).

The D02 long-term phase study found significant improvements from baseline HDRS scores in patients with treatment-resistant depression who received 12 months of VNS therapy. After the initial 10 weeks of treatment in the acute phase of the D02 study, changes to VNS device settings and concomitant treatments were permitted. The primary endpoint was changes over the 12-month study period in HDRS scores within 3-month quarters of equal weight. A repeated measures linear regression analysis found improvements in symptoms within all quarters, with a total of 52 patients (29.4%) demonstrating a significant treatment response. Of these 52 responders, 38 were considered “sustained” responders. However, a sustained response was defined somewhat more leniently than a general response in that HDRS score reductions from baseline at 9-, 10-, 11-, or 12-month follow-up could dip to $\geq$ 40% at two visits if a $\geq$ 50% improvement was noted at least once. Significant improvements in secondary endpoints, including the IDS-SR and MADRS, over 12 months were also noted. According to documentation filed with the FDA, this open-label continuation study represented the first step of an alternative statistical plan for demonstrating product effectiveness (FDA, 2005b). Such a protocol revision suggests an increased potential for bias that complicates the meaning of the reported results. Findings are also limited by the absence of a control group, which makes it difficult to differentiate a true treatment response from a placebo effect, particularly in a disorder with common variations in severity. Finally, the new protocols allowed for changes in concomitant

therapies throughout the study, and these therapies may have alleviated symptoms independent of VNS. However, this study does not rule out the possibility that some patients with severely refractory depression might benefit from VNS, and these findings should encourage initiation of a long-term RCT to further explore treatment potential.

A second study reported on the 24 months outcomes of the D02 study (Sackeim et al., 2007). The study defined those who had ≥ 50% improvement in $HDRS_{24}$ 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 of ≥ 40% rather than ≥ 50% in $HDRS_{24}$ 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 $HDRS_{24}$ 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.

Results from Uncontrolled Studies (evidence from uncontrolled studies unrelated to the RCT):

The D01 study initially enrolled 30 patients (Rush et al., 2000); an additional 30 patients were later enrolled (Sackeim, Rush et al., 2001). The longest follow-up for these patients was 2 years (Nahas et al., 2005; Sackeim et al., 2007).

In the initial report of the D01 study by Rush et al. (2000), 40% of patients achieved approximately a 50% improvement of $HDRS_{28}$ versus baseline, and 50% of patients experienced approximately a 50% improvement of MADRS compared with baseline values. Significantly more patients were in remission at 1 year (29%) than at 10 weeks VNS (17%) (P=0.046). No significant improvement in the secondary outcome measures was observed at 10 weeks VNS (n=30) or 1 year (n=28) for CGI-I (40%, 57%), GAF (baseline, 40.6; 10 weeks, 61.9; 1 year, 62.5), and YMRS (baseline, 2.3; 10 weeks, 1.9; 1 year, 2.4). The treatment effect was maintained for the complete follow-up of 1 year. At 1-year follow-up, responders experienced improvement in $HDRS_{28}$, MADRS, and CGI-I scores of 91%, 91%, and 91%, respectively; 64% of patients were in complete remission (Marangell et al., 2002).

In responders, MOS SF-36 mental component and physical function, social function, emotional role, mental health, physical role, and vitality subcomponents were significantly improved at 1 year compared with baseline values. In addition, mental

component and emotional role and vitality subcomponents were significantly improved from 1 year compared with 10 weeks of VNS therapy (P<0.05). In nonresponders, MOS SF-36 mental component, social function, mental health, and vitality components were significantly improved versus baseline and 3-month values (P<0.05) (Marangell et al., 2002).

Neurocognitive testing was performed in a small subset of patients (n=27) in the D01 study after 10 weeks of VNS. The study did not find evidence of deterioration in any neurocognitive measure, and some variables were improved compared with baseline (e.g., finger tapping, digit-symbol test, verbal fluency, logical reasoning, working memory, response inhibition, impulsiveness). The results suggest that VNS in treatment-resistant depression may be associated with stable and, in some instances, improved neurocognitive function. However, lack of a control or comparative group, small sample size, and short follow-up compromised the quality of this study (Sackeim, Keilp et al., 2001).

Nahas et al. (2005) and Sackeim et al. (2007) reported on a 24-month follow-up of patients enrolled in the D01 study; in the extension phase, patients were allowed to receive a variety of medications and ECT could be provided, and VNS parameters, such as current, frequency, and duty cycle, could be changed. Of 59 patients who were originally enrolled in the D01 study, 42 completed the full 24-month follow-up, and 81% were still using the device (Nahas et al., 2005). Response rate was 42% (25 of 59) after 2 years of VNS therapy, and remission rate was 22% (13 of 59) (Nahas et al., 2005). Sackeim et al. (2007) used a lower threshold for the primary outcome for the 2-year assessment, with treatment response defined as an improvement of at least 40% in $HDRS_{24}$ scores. According to Sackeim and colleagues, 30.5% of patients were VNS responders at 3 months ("early responders"), an additional 23.7% at 12 months ("late responders"), and 45.8% did not respond to the treatment. Overall, 72.2% of early responders maintained the treatment benefit for 12 months, and 61.1% of late responders were still responders at 24 months. Early and late responders experienced significantly greater improvement in $HDRS_{24}$ scores for the entire study period (61.6% and 60.8%, respectively) than nonresponders (24.5%) (P<0.0001). In both studies, most outcome measures indicated significant improvement from baseline. These findings give some indication that long-term VNS therapy may provide a benefit in some patients with treatment-resistant depression. If the treatment benefit would have been entirely attributable to a placebo effect, it is likely that the treatment effect would have worn off and that there would no longer be a difference in HDRS $scores_{24}$ between responders and nonresponders. However, controlled studies with adequate sample sizes are needed to confirm this observation. The results may have been confounded by the concomitant use of medications and ECT, thus the treatment effect of VNS cannot be determined from this study. Furthermore, the threshold that defined responders was lowered from ≥ 50% to ≥ 40% improvement in $HDRS_{24}$ scores for the long-term follow-up. Therefore, if the original threshold had been used, long-term response rates would likely be lower.

The D03 prospective, open-label, single-arm study investigated VNS as an adjunct to pharmacotherapy for treatment-resistant depression. The study enrolled 74 patients with treatment-resistant major MDD and bipolar disorder I or II (Schlaepfer et al., 2008). The study was conducted between 2001 and 2005. Patients received VNS for 12 months. Evaluated were improvements in symptoms of depression ($HDRS_{24}$, MADRS, IDS-SR) and complications, including the presence of mania (YMRS). The primary outcome measure was response rates, with response to treatment defined as ≥ 50% improvement in $HDRS_{24}$ scores. Remission was defined as $HDRS_{24}$ score of 10 or less. If the analysis was based on observed cases, 36% of patients were responders at 3 months and 55% responded to the treatment at 12 months. If a "last observation carried forward" analysis was used, response rates were 34% and 47% at 3 and 12 months, respectively. For both analyses, the response rates were statistically significant (*P*=0.000). The two other instruments measuring depression severity (MADRS and $IDS\text{-}SR_{30}$) also significantly improved. The mean improvement for the MADRS score was 41% after at 1 year. This was an uncontrolled open-label study; therefore, it is not possible to determine the extent of the treatment benefit.

Corcoran et al. (2006) published a short report on VNS results in 11 patients. The study was prospective, open-label, and uncontrolled. The center was part of the D03 study, and, therefore, it is possible that the 11 patients were part of this trial, although this is not explicitly mentioned in the article. The study followed the standard protocol used in the D01 to D04 series and lasted 12 months. Improvement in depression severity was measured using the $HRSD_{24}$, MADRS, and IDS-SR instruments. VNS improved the mean score of all three instruments. At 12 months, the $HDRS_{24}$ score was 19.27 points versus 36.36 at baseline (*P*=0.001); the respective values for the MADRS scores were 24.27 and 39.45 (*P*=0.013), and 31.81 and 57.81 for the IDS-SR instrument (*P*=0.002). The main limitations of this study were small sample size, the lack of a sham control, and rater blinding.

EVIDENCE FOR VNS FOR RAPID CYCLING BIPOLAR DISORDER (POSSIBLY D06 STUDY; see **Appendix IV**)

One small, prospective, open-label, uncontrolled study investigated VNS for the treatment of rapid cycling bipolar disorder (Marangell et al., 2008). Patients with this disorder had been excluded from most previous clinical studies. The study enrolled nine patients with ongoing manic, hypomanic, or depressive symptoms. The primary outcome measure was change in symptom severity (NIMH LCM-p); secondary outcomes included changes in symptoms of depression ($HDRS_{28}$, $HDRS_{24}$, $IDS\text{-}SR_{30}$, MADRS), CGI, symptoms of mania and hypermania (YMRS), and function (GAF). There was a significant improvement in all outcome measures except $IDS\text{-}SR_{30}$ (for absolute and for % change) scores and YMRS (for % change). The respective mean improvements were 27.3% and 38.3% for symptoms of depression assessed with the $HDRS_{24}$ and MADRS scales, respectively, 20.6% clinical improvement measured with CGI, and 21.4% for physical and mental functioning assessed with the GAF instrument. This was an uncontrolled, open-label study, and the sample size was very small; therefore, the results cannot be generalized, and additional well-controlled trials are

needed to confirm whether the treatment effect seen in this study can be attributed at least in part to VNS.

Effectiveness Summary: Overall, there is insufficient evidence to conclude that VNS improves depression, quality of life, and function in patients with treatment-resistant MDD and bipolar disorders. The only double-blind RCT, lasting 12-weeks, could not demonstrate a statistically significant difference in the primary outcome measures; a statistically significant difference was noted in only one secondary outcome measure. The results of a nonrandomized study comparing VNS plus standard treatment to standard treatment alone were also conflicting. While the primary data analysis of this study suggested that VNS plus standard treatment was superior to standard treatment alone, there was significant heterogeneity among groups confounding the results, and, if the analysis was adjusted to account for these differences, significance was lost. Results from the long-term uncontrolled studies suggest that patients who respond to the treatment at 3 or 12 months are likely to maintain the response for up to 24 months. While this result suggests a possible treatment benefit beyond a placebo effect because a placebo effect would normally wear off earlier, a concern with these studies is that they used lower the threshold for the definition of responders; therefore, if the response rates had been based on the original threshold, actual long-term response rates might be lower.

2. Are vagus nerve stimulators safe?

There were only 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 and included worsening of depression, asystole, and bradycardia.

Safety data were available for a time frame of up to 2 years, and all longer-term data were from uncontrolled studies. 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. Some complications were serious and/or required hospitalization, including: suicide, attempted suicide, and suicide ideation; worsening of depression; manic episodes; agitation; hypomania; CNS toxicity; asystole; bradycardia; syncope; venous thrombophlebitis; nephrolithiasis; cholelithiasis; and pulmonary embolism (Marangell et al., 2008; Rush, Marangell et al., 2005; Rush, Sackeim et al., 2005; Sackeim, Rush et al., 2001; Schlaepfer et al., 2008). While adjusting the stimulation parameters reversed some complications such as voice alterations, other complications (e.g., dyspnea, pain) required treatment or were permanent.

There was no overall statistically significant difference; however, several cardiovascular events occurred in the clinical studies that may have been related to VNS therapy. In

the RCT (D02 trial, n=235), the following cardiovascular events may have been related to VNS therapy: arrhythmia (1), asystole (1), hypotension (1), bradycardia (2), palpitation (8), syncope (4), dizziness (11), and vasodilatation (4). In the uncontrolled D01 trial (n=60), four episodes of palpitations and six episodes of dizziness may have been related to cardiac stimulation (FDA, 2005b). In the uncontrolled D03 study (n=47), syncope (2) was the only cardiovascular complication. One death of unknown cause occurred in the RCT (D02 trial). An autopsy was not performed, and a causal relationship between VNS therapy could, therefore, not be confirmed nor excluded.

Worsening of depression, suicide, and suicide ideation associated with VNS therapy also occurred; however, a causal relationship between these incidents and VNS therapy has not been established. In the D04 study, a comparative analysis of VNS therapy (data from D02 trial) versus standard depression therapy, there was no statistically significant difference in depressed mood and suicidal ideation between these two groups. However, this result is not based on a randomized clinical study but on a comparison between two separate studies. The preliminary results suggest that VNS therapy may not worsen depression and suicidal ideation beyond what is observed with standard treatment.

Safety Summary: Safety data were available for a time frame of up to 2 years, and all longer-term data were from uncontrolled studies. In the clinical studies, patients experienced the following complications that may have been related to VNS or electrode implantation: pain, headache, abnormal wound healing, edema, infection, pharyngitis, dyspnea, coughing, dysphagia, dyspepsia, nausea, tooth disorder, dizziness, twitching, insomnia, rash, palpitations, and generalized spasms. Some complications were serious and/or required hospitalization, including: suicide, attempted suicide, and suicide ideation; worsening of depression; manic episodes; agitation; hypomania; 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 in the clinical studies that may have been related to VNS therapy, suggesting that VNS may cause cardiovascular complications. Worsening of depression, suicide, and suicide ideation associated with VNS therapy also occurred. The results from a nonrandomized controlled study of VNS versus standard therapy (D04 study) suggest that VNS therapy may not worsen depression and suicidal ideation beyond what is observed with standard treatment.

3. Does effectiveness vary by age, response to antidepressants, or other patient characteristics?

The effectiveness of VNS for these types of depression has not been unequivocally demonstrated in controlled studies. The clinical trials have enrolled patients with chronic, severe, treatment-resistant MDD and bipolar disorders, and VNS has not been investigated for other types of depression. While some patients respond to the

treatment, it is unknown whether the response is due to a treatment effect or is a placebo response. Possible predictors of a positive treatment response that could be tested in clinical studies have not yet been identified. Therefore, patient selection criteria for VNS in patients with treatment-resistant depression have not yet been established and it is not known who could benefit from the treatment.

Nierenberg, Alpert, Gardner-Schuster, Seay, & Mischoulon (2008) compared outcomes for unipolar versus bipolar disorder for a 12 months time frame using data from of 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 ($HDRS_{24}$, $ISD\text{-}SR_{30}$), 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.

There is insufficient data to determine which patients with treatment-resistant depression would benefit from VNS, and it is not clear whether any possible treatment response varies among patients according to factors such as age, sex, disease severity, and type of depression.

Summary of Patient Selection Criteria: The effectiveness of VNS for depression is not yet proven. At present, it is not possible to determine which patients with treatment-resistant depression would benefit from VNS, and it is not clear whether any possible treatment response varies among patients according to factors such as age, sex, disease severity, and type of depression.

Strengths and Limitations of the Evidence

Overall, the available evidence evaluating the efficacy of VNS in the treatment of patients with chronic, severe, treatment-resistant MDD and bipolar disorders was of low quality. There was only one randomized controlled trial (RCT) of good quality (Carpenter et al., 2004; Rush, Marangell et al., 2005). There were three nonrandomized controlled studies that provided poor-quality evidence (two studies) or fair-quality evidence (one study); two of the studies reported on the same patients as the RCT and, therefore, did not provide new evidence (George et al., 2005; Nierenberg, Alpert, Gardner-Schuster, Seay, & Mischoulon, 2008; Sperling, Reulbach, & Kornhuber, 2009). The remaining evidence was derived from uncontrolled studies of poor to fair quality. The assigned quality ratings can be viewed in the evidence table. A low quality rating was assigned to the overall body of evidence because of sparse data and design limitations.

There was significantly more evidence available for MDD than bipolar disorder. Only one small, prospective, open-label, uncontrolled study evaluated VNS for rapid cycling bipolar disorder, possibly the D06 study (Marangell et al., 2008). Assessing treatment efficacy in depression is always based on patient-assessed and physician-assessed outcome measures with their inherent subjective bias; however, most studies used rigorous testing based on several standard instruments to estimate depression severity, quality of life, and disability, including sufficient redundancy to minimize the effect of personal bias, thus strengthening the quality of the studies. In the D01 to D04 studies, the primary measure of efficacy was a ≥ 50% improvement of Hamilton Depression Rating Scale (HDRS) baseline scores (D01, $HDRS_{28}$; D02, D03, D04, $HDRS_{24}$); patients who experienced this level of improvement were considered responders. The studies enrolled patients with chronic, severe depression, generally defined as a mean baseline total HDRS score ≥ 20, with a ≥ 50% improvement considered clinically meaningful. Patients who achieved an $HDRS_{28}$ score of ≤10 were considered to be in remission. These are clinically meaningful outcomes in patients with chronic severe depression. However, after the results of the D02 study did not show a significant difference for VNS versus control, the investigators revised the statistical plan to include additional analyses. This revised statistical plan was used for the analysis of the D02 unblinded long-term follow-up and for a comparison of VNS therapy with standard treatment (see D04 study results, **Appendix IV**). Based on the revised statistical plan, including a regression analysis of HDRS scores over time, the investigators reported a statistically significant improvement in the mean change in HDRS over 12 months on active VNS versus sham VNS. The authors also lowered the threshold for the definitions of "responders" from ≥ 50% to ≥ 40% mean changes in HDRS scores (Sackeim et al., 2007). This increased the percentage of responders in the longer-term follow-up, and it is not clear whether a threshold of 40% is still considered clinically significant. Additional secondary outcomes included MADRS, YMRS, CGI-I, CGI-S, GAF, MOS SF-36, and YMRS scores, and strengthened the quality of the studies. The studies measured absolute and relative changes in the scores for these instruments.

Several factors limited the quality of individual studies and the overall body of evidence. Lack of a control or comparative group was the major limiting factor of all but three studies; only one of these controlled trials used randomization (Rush, Marangell et al., 2005). In consideration of a substantial placebo effect associated with depression treatment, the results can only be regarded as preliminary. Control patients in the D02 study did not receive stimulation. VNS can be felt, and any placebo-controlled VNS trial that does not include a low dose of stimulation jeopardizes blinding. Stimulation parameters varied among patients, which may have affected treatment outcomes, and concomitant medications and procedures were allowed for several of the study phases, which confounds evaluation of the treatment effect of VNS. Sample sizes were small across studies, ranging from 9 to 235 patients; sample sizes were very small for patient subpopulations such as those with bipolar and rapid cycling bipolar disorder. Finally, as the technology is in use for depression for a relatively short time, long-term data on safety and efficacy are not yet available. The device manufacturer supported most of the studies, and several of the investigators disclosed financial ties to the manufacturer, which introduces the potential for investigator bias.

Since VNS stimulation is provided automatically, and patient compliance is not an issue. However, some patients were lost to follow-up in the longer-term studies. There was a lack of data comparing VNS with ECT; therefore, no conclusions are possible regarding the comparative efficacy of VNS and ECT.

Lack of controls, small sample sizes, and the short follow-up in the controlled study limited the evidence for safety assessments. There was a lack of studies investigating predictors for a positive treatment benefit. In the one study that compared VNS for the treatment of bipolar versus unipolar depression, there was no difference in changes in depression. However, the sample size for the bipolar group was very small, and the study did not have sufficient power to prove equivalence of VNS for both indications. Therefore, a lack of superiority of VNS for one indication over the other does not demonstrate equality of VNS for both indications.

Table 1. Primary Studies Assessing Vagus Nerve Stimulation for Depression

Key: ATHF, Antidepressant Treatment History Form; BDI, Beck Depression Inventory; CGI-I, Clinical Global Impressions-Improvement Index; CGI-S, Clinical Global Impressions-Severity Index; CNS, central nervous system, DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; dx, diagnosis; ECT, electroconvulsive therapy; f/u, follow-up; GAF, Global Assessment of Function; grp(s), group(s); HDRS, Hamilton Depression Rating Scale; $HDRS_{28}$, 28-item Hamilton Depression Rating Scale; $HRSD_{24}$, 24-item Hamilton Rating Scale for Depression; hx, history; $IDS\text{-}SR_{30}$, 30 item Inventory of Depressive Symptomatology-Self-Report; IQ, intelligence quotient; LOCF, last observation carried forward; LOS, length of stay; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MDE, major depressive episode; MOS SF-39, Medical Outcomes Study Short Form-36 Health Survey; NCP, NeuroCybernetic Prosthesis; NIMH LCM-p, National Institute of Mental Health prospective Life Charting Method; NR, not reported; NS, not statistically significant; pt(s), patient(s); QOL, quality of life; RCT, randomized controlled trial; stim, stimulation; TAU, treatment as usual; tx, treatment (or therapy); VNS, vagus nerve stimulation; YMRS, Young Mania Rating Scale

Authors/Study Design	Study Population	Treatment Protocol	Results	Conclusions/Limitations/ Quality Ratings
Randomized, controlled Trials				
Rush, Marangell et al. (2005)* 21 VNS study centers in U.S. and Canada Double-blind, randomized, parallel-grp, sham-controlled study (D02, acute phase) *F/u:* 10 wks *Funding:* Cyberonics Inc.	n=266 pts *Inclusion criteria:* DSM-IV primary dx of a major depressive disorder or bipolar I or II disorder; recurrent or chronic depressive episode ≥2 yrs or at least 4 lifetime major depressive episodes, refractory to ≥2 but ≤6 standard antidepressant medications; mean baseline total HDRS score ≥20; pts w/ bipolar disorder had to be resistant to or intolerant of lithium *Exclusion criteria:* Pregnancy; atypical or psychotic features; lifetime hx of any nonmood psychotic disorder; current rapid-cycling bipolar disorder; current secondary dx of delirium, dementia, amnesia, or other cognitive disorder; clinical significant	235 pts were implanted w/ VNS device; 222 pts were available for analysis. Pts were randomly assigned to 2 grps: active VNS (n=112) and sham VNS (n=110). All pts underwent NCP device implantation followed by 2-wk single-blind recovery period in the off-stim state. At wk 2, pts in active tx grp received VNS for 10 wks; control grp did not receive stim but underwent similar programming procedure. Pts were allowed concomitant medications if medication type and dose were stable during study period. Outcomes were assessed at wks 2 and 12. *Outcome measures:*	Clinical outcomes after 10 wks of tx (active VNS; sham VNS): *Response rate (%):* $HDRS_{28}$: 15.2%; 10.0% (NS) MADRS: 15.2%; 11% (NS) CGI-I: 13.9%; 11.8% (NS) $IDS\text{-}SD_{30}$: 17.0; 7.3% (*P*=0.032) *Improvement from baseline (%):* $HDRS_{28}$: 16.3%; 15.3% (NS) MADRS: 17.1%; 12.4% (NS) $IDS\text{-}SD_{30}$: 21.2%; 16.3% (NS) *Complications:* Device explantation due to infection (1 pt, active VNS grp): suicide (1 pt, active VNS grp). Other adverse events were similar for both grps and included worsening of depression, asystole, and bradycardia.	Results failed to demonstrate a benefit of active VNS compared w/ sham VNS for pts w/ tx-resistant depression. *Limitations:* Short duration of tx; concomitant medications allowed; VNS stim parameters not standardized. *Quality:* Good

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	current suicidal intent; contraindications to surgical implantation of VNS device	$HDRS_{28}$ Response Rate and % Improvement from Baseline, MADRS Response Rate and % Improvement from Baseline, CGI-I Response Rate, IDS- SR_{20} Response Rate and % Improvement from Baseline, MOS SF-36; response defined as 50% improvement of $HDRS_{28}$ baseline score		
Carpenter et al. (2004)* Butler Hospital, Brown University School of Medicine, Providence, Rhode Island; University of Arizona, Tucson, AZ; Baltimore Veterans Affairs Medical Center; University School of Medicine, Baltimore, MD; Yale University, New Haven, CT Double-blind, randomized, parallel-grp, sham-controlled study (analysis of subset of pts from D02 study) *F/u:* 24 wks	n=21 pts (subgrp of 205 pts enrolled in D02 study; mean age 48 yrs; 11 women, 10 men) *Inclusion criteria:* Pts w/ recurrent or chronic depressive episode, refractory to ≥2 but ≤6 standard antidepressant medications; mean baseline total $HDRS_{24}$ score ≥20 *Clinical hx:* Unipolar 18 (85.5%); bipolar 3 (14.3%)	Pts were randomly assigned to 2 grps, active and sham VNS. All pts underwent NCP device implantation followed by 2-wk single-blind recovery period in the off-stim state. At wk 2, pts in active tx grp received VNS; control grp did not receive stim but underwent similar programming procedure. At wk 12, pts in active grp continued to receive VNS w/ optional adjustment of stim parameters (active-VNS grp); pts in sham grp who were still depressed had option to cross over to active tx grp (sham-VNS grp). Outcomes were assessed at wks 2, 12, and 24. *Outcome measures:* HDRS*24*, CGI-S, CGI-I, cerebral spinal fluid analyte concentrations	Clinical outcomes (total, sham-VNS, active-VNS): *$HDRS_{24}$:* Wk 2: 28.2, 29.8, 26.8 (NS) Wk 12: 23.5, 26.3, 21.0 (NS) Wk 24: 20.6, 24.0, 17.5 (NS) *CGI-S:* Baseline: 4.9, 4.9, 4.9 (NS) Wk 2: 4.9, 4.9, 4.9 (NS) Wk 12: 4.7, 4.9, 4.5 (NS) Wk 24: 4.2, 4.8, 3.7 (NS) *CGI-I (n) (%):* Wk 12: Much/very much: 2 (9.5%); 0; 2 (18.1%) (NS) Minimal to worse: 19 (90.5%); 10 (100%); 9 (81.2%) (NS) Wk 24: Much/very much: 4 (19.0%); 1 (10.0%); 3 (27.3%) (NS) Minimal to worse: 17 (81.0%); 9 (90.0%); 8 (72.7%) (NS) Significant tx effect of VNS was observed for homovanillic acid concentration (sham-VNS, active-VNS) (mean change in 2-12 wks): –9.4%, 18.8% (*P*=0.03)	Results demonstrated that VNS might increase cerebrospinal fluid homovanillic acid concentrations, which is suggestive of an effect on CNS metabolism and, thus, function. However, this effect was not reflected in the clinical outcomes. VNS may not be effective for tx of unipolar and bipolar forms of depression. *Limitations:* Very small sample size; sample represents subgrp selected from larger clinical trial, purpose of analysis to measure surrogate outcomes such as changes in levels of brain chemicals *Quality:* Fair (downgraded from good because of very small sample size and focus on surrogate outcome measures)

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Funding: Cyberonics Inc.		(sample obtained by lumbar puncture)	Mean gamma-aminobutyric acid, norepinephrine, 5-hydroxyindoleacetic acid, and 3-methoxy-4-hydroxyphenylglycol concentrations were not significantly affected. *Complications:* NR	
Nierenberg, Alpert, Gardner-Schuster, Seay, & Mischoulon (2008)* 21 VNS study centers in U.S. and Canada Double-blind, randomized, parallel-grp, sham-controlled study, including 2-yr extension study (post hoc analysis of subset of pts from D02 study (unipolar vs bipolar depression) *F/u:* 2 yrs *Funding source:* Cyberonics Inc.	n=235 pts; 177 pts completed the 12-mos protocol. *Inclusion criteria:* See Rush et al. (2005a); pts w/ unipolar and bipolar depression who participated in D02 trial *Exclusion criteria:* See Rush, Marangell et al. (2005); pts w/ rapid cycling bipolar disorder *Clinical hx (%pts):* DSM-IV bipolar I or bipolar II disorder (11%)	See Rush et al. (2005a) During RCT (acute phase), 13 pts w/ bipolar depression and 104 pts w/ unipolar depression received active tx (stim-on). Response defined as ≥50% decrease in baseline HDRS or IDS scores and YMRS score <12. *Outcome measures:* Changes in depression in pts w/ unipolar vs bipolar depression and QOL ($HDRS_{24}$, IDS-SR, YMRS, MOS-36)	Differences between unipolar and bipolar depression NS for all outcomes. During 24 mos f/u, 7 pts w/ bipolar and 52 pts w/ unipolar depression had withdrawn from study. Improvement in respective score at 24 mos f/u ≥50% to <75% and ≥75% (# pts, % pts): *$HDRS_{24}$:* Unipolar: 34 (24%); 12 (9%) Bipolar: 3 (19%); 3 (19%) *IDS-SR ≥50%-<75% improvement:* Unipolar: 29 (21%); 7 (5%) Bipolar: 7 (44%); 1 (6%) *MOS–36 physical and mental component (# pts, median change) at 12 mos:* Unipolar: 94, –2.05, 8.39 Bipolar: 09, –6.18, 10.54 *YMRS acute phase (baseline, 6 wks, 12 wks) (continuous mean YMRS score):* Unipolar (points): 2.377, 1.949, 1.998 Bipolar (points): 1.673, 2.280, 2.180	Study did not demonstrate a difference in improvement of depression and QOL between pts w/ unipolar and bipolar depression. Study was not designed to test for equality of VNS in both pt populations, and results do not permit conclusions regarding the comparative efficacy of VNS in these pts. *Limitations:* Post hoc analysis; lack of control grp for long-term f/u; very small sample size for pts w/ bipolar depression; power of the statistical comparison NR; heterogeneity between pt grps w/ regard to hx of antidepressant-induced mania, duration of MDD episodes, episodes of chronic depression lasting ≥2 yrs, # of MDD episodes during lifetime; pts varied significantly regarding type and quantity of antidepressant tx; many medication changes during long-term f/u. *Quality:* Poor (downgraded from fair because of small

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				sample size for bipolar disorders and a large # of pts who had w/drawn from the study)
Nonrandomized, controlled studies				
George et al. (2005)* Multiple medical centers in U.S. and Canada, including some of the VNS study centers D04 trial: Comparison of D02 extension study data (see Rush et al., 2005b) w/ data from observational study of tx as usual (TAU) for tx-resistant depression *F/u:* 1 yr *Funding:* Cyberonics Inc.	n=205 pts in D02 study (mean age 46.3 yrs; 36% men, 64% women) n=124 pts in TAU study (mean age 45.5 yrs; 32% men, 69% women) *Inclusion/exclusion criteria:* Similar for both D02 and observational study; see Rush, Marangell et al. (2005) for D02 study criteria *Clinical hx:* D02 study: Unipolar 90%; bipolar 10% TAU study: Unipolar 88%; bipolar 12%	Tx protocol for D02 study described by Rush, Sackeim et al. (2005) and Rush, Marangell et al. (2005). Observational TAU study involved quarterly assessments of pts receiving a variety of medications, psychotx, and nonpharmacological tx such as ECT. *Outcome measures:* $HRSD_{24}$; $IDS\text{-}SR_{30}$; CGI-I	*Clinical outcomes for180 pts in VNS grp and 112 pts in TAU study w/ 12-mo data (VNS study; TAU study):* Avg change in IDS-SR: –9.8; –4.6 50% improvement in IDS-SR: 22%; 12% Final IDS-SR <14: 15%; 4% Avg change in $HRSD_{24}$: –8.2; –4.9 50% improvement in $HRSD_{24}$: 30%; 13% Final $HRSD_{24}$ <9: 17%; 7% CGI-I 1 or 2: 37%; 12% (All measures *P*<0.04) *Clinical outcomes for all pts (LOCF) (VNS study; TAU study):* Average change in IDS-SR: –9.3; –5.0 50% improvement in IDS-SR: 20%; 12% Final IDS-SR <14: 3%; 3% Avg change in $HRSD_{24}$: –7.4; –4.9 50% improvement in $HRSD_{24}$: 27%; 13% Final $HRSD_{24}$ <9: 17%; 7%; 19.6; 20.6 CGI-I 1 or 2: 34%; 12% (All measures *P*≤0.04)	Results suggest that VNS may provide greater improvement in symptoms compared w/ usual tx for pts w/ tx-resistant depression. *Limitations:* Control data from a separate study (TAU study); VNS and TAU study populations may not be comparable; VNS pts received concomitant txs, which confounds evaluation of VNS tx effect. *Quality:* Fair
Sperling, Reulbach, & Kornhuber (2009) University Hospital of Erlangen, Erlangen, Germany	n=18 pts Control grp (sex-matched and age-matched): n=9 pts (mean age 50 yrs; 5 women, 4 men) VNS grp: n=9 pts (mean age 50 yrs; 5 women, 4	Control grp: Received psychotropic medication and psychotherapy VNS grp: Received VNS as an adjunct to psychotropic medication *Outcome measures:*	NS difference in baseline characteristics between grps. Mean $HDRS_{28}$ score in VNS grp was significantly reduced from 23.7±2.4 points at baseline to 10.2±2.4 points at 12 mos (*P*<0.001). NS change in the control grp (data NR in text, only graphic presentation).	Results indicate that VNS as an adjunct to medical tx improves symptoms of depression, decreases LOS, and reduces # of psychiatric txs in pts w/ MDD compared w/ medical tx + psychotherapy.

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Prospective, nonrandomized, open-label, controlled study to evaluate VNS for MDD *F/u:* 12 mos *Time frame:* 2002-2005 *Funding source:* NR	men) *Inclusion criteria:* Pts w/ tx-resistant MDD *Exclusion criteria:* NR	Changes in symptoms of depression ($HDRS_{28}$); LOS; # psychiatric txs/yr; cost (see ***Economic Evaluations***)	VNS significantly reduced LOS from 65±15.2 days to 44±7.4 days per yr. In the control grp, LOS remained constant (only graphic presentation of control data). VNS significantly reduced # of psychiatric txs/yr from 33±3.9 to 14±2.2 at 12 mos. There was no statistically significant change in the control grp. The respective values for the control grp were 24.9±6.8 at baseline to 25.3±8.1 at 12 mos. *Complications:* NR	Result needs to be confirmed in a larger placebo-controlled study. *Limitations:* Small sample size; lack of placebo-controlled study; lack of blinding and randomization; only 1 instrument assessed symptoms of depression. *Quality:* Poor
Uncontrolled studies				
Rush et al. (2000)*† University of Texas Southwestern Medical Center, Baylor College of Medicine, Dallas, TX; Medical University of South Carolina; Ralph H. Johnson Veterans Hospital, Charleston, SC; New York State Psychiatric Institute, New York, NY Multicenter, nonrandomized, open-label, single-arm study (D01) *F/u:* 10 wks	n=30 pts (mean age 47.5 yrs; 67% women, 33% men; mean duration of illness 19.3 yrs) *Inclusion criteria:* Age 18-70 yrs; DSM-IV dx or bipolar I or II disorder (APA, 1994); MDE ≥2 yrs duration or ≥4 MDE in his/her lifetime; stable dose for ≥4 wks prior to 1st baseline visit if on medication; score ≥3 on ATHF, refractory to ≥2 antidepressant medication txs from different medication classes during the current MDE; unsuccessful psychotx for ≥6 wks; score ≥20 on $HDRS_{28}$; score ≤50 on GAF; have IQ ≥70; pts w/ bipolar disorder had to have resistance or intolerance or medical intolerance to	NCP device implantation was followed by 2-wk single-blind recovery period in the off-stim state. Pts had to score ≥18 on $HDRS_{28}$ at 7 and 14 days postsurgery before stim was initiated. During the following 2 wks, output current was progressively increased to maximum level still comfortable to the pt. VNS was delivered for a total of 10 wks. Outcomes were assessed twice w/in 4 wks of baseline. *Outcome measures:* $HDRS_{28}$, MADRS, YMRS, CGI-I, CGI-S, GAF, MOS SF-36, YMRS; remission was defined as $HDRS_{28}$ score ≤10	Responders (≥50% improvement of $HDRS_{28}$ baseline score): 12 (40%) Responders (≥50% improvement of MADRS baseline score): 15 (50%) Pts in remission: 16.7% Time to response: Range 1-10 wks Lower stim parameters appeared to be more effective. Clinical outcomes (baseline, off-stim, 10 wks on-stim; response rate): $HDRS_{28}$: 38.0, 36.6, 23.0; 40% MADRS: 33.8, 32.5, 20.1; 50% CGI-I: NR, 0%, 40%; 40% CGI-S: 5.3, 5.1, 3.7; NR GAF: 40.6, 43.2, 61.9; 40% YMRS: 2.3, 2.2, 1.9; NR MOS SF-36 physical component and 2 subcomponents (pain index, health perception) remained similar throughout trial for all pts. In responders, mental component and 5 subcomponents (role function, vitality, social function, emotional role, mental health) improved significantly (P<0.05). In	Results suggest that VNS may provide symptom relief in some pts (40%) w/ standard tx-resistant MDD or bipolar disorders. A small proportion of pts (17%) may experience complete symptom remission. *Limitations:* Lack of control or comparison grp; w/ the exception of a short, single-blind phase, blinding was not performed; small sample size; lack of power analysis; short f/u. *Quality:* Poor

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(acute); ≥12 mos *Funding source:* Cyberonics Inc.	lithium *Exclusion criteria:* Pregnant or did not use acceptable birth control methods; atypical or psychotic features in current MDE; hx of nonmood disorder psychosis; rapid-cycling bipolar disorder; current secondary dx of cognitive disorders; current, clinically significant suicidal intent; risk related to surgical implantation and VNS *Clinical hx:* MDD recurrent (50%); MDD single episode (20%); bipolar I disorder (13%); bipolar II disorder (17%); current MDE ≥2 yrs (70%)		nonresponders, only social function subcomponent improved (P<0.05); all other items remained stable. 3/12 responders achieved exit role emotional values that were similar to or exceeded those of population norm. *Complications (# surgery related; VNS-related possible, probable, definite):* Incision site pain (9; 0, 0, 0); headache (2; 5, 0, 2); pain (2; 0, 2, 3); chest pain (1; 3, 0, 1); neck pain (0; 1, 2, 2); infection (2; 0, 0, 0); voice alterations (2; 1, 3, 12); pharyngitis (1; 2, 4, 1); dyspnea (1; 2, 3, 1); coughing (0; 0, 1, 3); dysphagia (1; 0, 1, 3); dyspepsia (2; 0, 1, 0); nausea (1; 2, 0, 0); dizziness (0; 3, 0, 0); hypertonia (1; 0, 0, 2); twitching (0; 0, 2, 0); rash (1; 2, 0, 0); abnormal healing (3; 0, 0, 0); edema (2; 0, 0, 0); ear pain (0; 2, 0, 0)	
Sackeim, Rush et al., (2001)† New York State Psychiatric Institute, New York, NY Multicenter, nonrandomized, open-label, single-arm study – study extension (D01) (Rush et al., 2000) *F/u:* 10 wks (acute) *Funding source:*	n=60 (mean age 46.8 yrs, range 20.7-63.1; 65% women, 35% men; duration of illness 18.1 yrs); n=30 were enrolled in an earlier trial (see Rush et al., 2000); in this study, an additional 30 pts were enrolled *Inclusion criteria:* See Rush et al. (2000) *Exclusion criteria:* See Rush et al. (2000) *Clinical hx:* MDD recurrent (47%); MDD single episode (27%); bipolar I disorder (10%); bipolar II disorder	See Rush et al. (2000)	Data available for 59 pts. Responders (≥50% improvement of $HDRS_{28}$ baseline score): 30.5% Responders (≥50% improvement of MADRS baseline score): 34% Pts in remission: 15.3% Mean time to response: 48.1 days *Clinical outcomes (baseline, off-stim, 10 wks on-stim; response rate):* $HDRS_{28}$: 36.8, 35.0, 24.7; 32% MADRS: 33.4, 32.0, 22.9; 29.9% CGI-I: NR, 0%, 37%; NR CGI-S: 5.2, 5.0, 3.9; 23.0% GAF: 40.6, 43.0, 57.4; 43.7% YMRS: 2.3, 2.2, 1.9; -12.3% BDI: 34.9, 32.6, 23.0; 32.6% Response rate in 2nd grp of 29 pts (n=6,	Results demonstrated a tx effect in limited # of pts, ranging from 30%-37%, depending on parameters used to define clinical success. *Limitations:* Lack of control or comparison grp; w/ the exception of a short, single-blind phase, blinding was not performed; lack of power analysis. *Quality:* Poor

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Cyberonics Inc.	(17%)		20.7%) was lower than in 1st study (n=12, 40%) (Rush et al., 2000); however, this difference did not reach statistical significance (*P*=0.158). Demographic data similar for both grps. *Complications (n, % of pts):* The following complications occurred in ≥5% of pts and may have been related to VNS or electrode implantation: incision site pain (18, 30%); headache (13, 22%); pain (9, 13%); chest pain (4, 7%); neck pain (10, 17%); wound abnormality (4, 7%); infection (3, 5%); voice alterations (33, 55%); pharyngitis (8, 13%); dyspnea (9, 15%); coughing (10, 17%); dysphagia (8, 13%); dyspepsia (6, 10%); nausea (4, 7%); tooth disorder (3, 5%); dizziness (3, 15%); twitching (3, 5%); insomnia (3, 5%); rash (4, 7%); abnormal healing (3, 5%); palpitations (3, 5%); generalized spasms (0, 0%).	
Sackeim, Keilp et al., (2001)† New York State Psychiatric Institute, New York, NY Multicenter, nonrandomized, open-label, single-arm study (D01) *F/u:* 10 wks *Funding source:* Cyberonics Inc.	n=27 (mean age 47.7 yrs, range 28.6-63.1; 19 women, 8 men) *Inclusion criteria:* See Rush et al. (2000) *Exclusion criteria:* See Rush et al. (2000)	See Rush et al. (2000) Outcomes assessed at baseline and after 10 wks of stim. *Outcome measures:* Neurocognitive tests	Neurocognitive outcomes: Mean change at 10 wks vs baseline (*P*=10 wks vs baseline): *Motor function scores:* Finger tapping (n=27): Dominant hand: –2.6 (NS) Nondominant hand: –1.7 (NS) Simple reaction time (n=21): 22.5 (NS) Choice reaction time (n=24): 2.1 (NS) *Psychomotor function scores:* Digit symbol (n=27): Raw score: –5.7 (*P*=0.002) Scaled score: –1.1 (*P*=0.0003) Trail making (n=20) (time, secs): Trail A: 8.9 (*P*=0.02) Trail B (time, sec): 4 (NS) *Language scores (n=26):* Controlled Oral Word Association: –3.9 (*P*=0.02) *Executive function:* A, not B reasoning (n=23): Reaction time: 543.5 (*P*=0.02)	Results suggest that VNS for tx-resistant depression is associated w/ stable and, in some instances, improved neurocognitive function. *Limitations:* Lack of control or comparison grp; w/ the exception of a short, single-blind phase, blinding was not performed; small sample size; lack of power analysis; short f/u. *Quality:* Poor

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			Correct responses: –0.4 (NS) N-back (n=23): Correct 1-back: –0.01 (NS) Correct 2-back: –0.7 (*P*=0.04) Correct 3-back: –1.7 (*P*=0.005) RT 1-back: –17.9 (NS) RT 2-back: 82.1 (NS) RT 3-back: 20.5 (NS) Go, no go (n=21): Correct response: –2.8 (*P*=0.049) Commission errors: 0.8 (NS) Reaction time: –10.8 (NS) Attention: NS changes were observed for Continuous Performance Test (n=23) and Stroop Effect (n=24). Memory (n=26): NS changes were observed for Buschke Selective Reminding Test and Benton Visual Retention Test.	
Marangell et al. (2002)† Baylor College of Medicine, Houston, TX Multicenter, nonrandomized, open-label, single-arm study (D01) *F/u:* 1 yr *Funding source:* Cyberonics Inc.	n=30 pts (see Rush et al., 2000)	See Rush et al. (2000)	Device was removed due to lack of efficacy in 1 pt at 11 mos. Responders (≥50% improvement of $HDRS_{28}$ baseline score): 12 (40%) Responders (≥50% improvement of MADRS baseline score): 15 (50%) Pts in remission (3 mos, 1 yr): 17%, 29% (*P*=0.046) *Clinical outcomes (baseline, 10 wks on-stim, 1 yr; response rate 10 wks, 1 yr) (P-value 1 yr vs acute):* # of pts: 30, 30, 28 $HDRS_{28}$: 38.0, 23.0, 19.7; 40%, 46% (*P*=0.008) MADRS: 33.8, 20.1, 16.6; 50%, 50% (NS) CGI-I: 5.3, 3.7, 3.4; 40%, 57% (NS) GAF: 40.6, 61.9, 62.5; NR; NR YMRS: 2.3, 1.9, 2.4; NR, NR *Response rates (%) for various outcome measures for responders (3 mos, 1 yr); nonresponders (3 mos, 1 yr):* Number of pts: 12, 11; 18, 17	*Limitations:* Lack of control or comparison grp; w/ the exception of a short, single-blind phase, blinding was not performed; small sample size; lack of power analysis. Quality: Poor

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			$HDRS_{28}$: 100%, 91%; 0, 18% MADRS: 100%, 91%; 17%, 24% CGI-I: 92%, 91%; 6%, 35% Remission: 42%, 64%; 0, 6% In responders, MOS SF-36 mental component and physical function, social function, emotional role, mental health, physical role, and vitality subcomponents were significantly improved at 1 yr f/u vs baseline; mental component, emotional role, and vitality subcomponents were significantly improved at 1 yr vs 3 mos (P<0.05). In nonresponders, MOS SF-36 mental component, social function, mental health, and vitality were significantly improved vs baseline and 3-mo values (P<0.05). *Complications (% pts at 1 yr):* The following complications may have been related to VNS or electrode implantation: severe complications requiring hospitalization (2) included hypomania (1) and deep venous thrombophlebitis (1). Mild complications included voice alterations (21%), dyspnea (7%), neck pain (7%), headache (3%), dysphagia (3%), nausea (3%), and tooth disorder (3%).	
Nahas et al. (2005)† Medical University of South Carolina; Ralph H. Johnson Veterans Hospital, Charleston, SC; Baylor College of Medicine, Houston, and University of Texas Southwestern	n=60 (mean age 46.8 yrs, range 20.7-63.1; 65% women, 35% men; duration of illness 18.1 yrs) (see Sackeim et al., 2001a) *Inclusion criteria:* See Rush et al. (2000) *Exclusion criteria:* See Rush et al. (2000) *Clinical hx:* MDD recurrent	See Rush et al. (2000); 59 pts received VNS After 12-wk acute phase, medications could be changed in type or dose and ECT could be provided, and VNS parameters could also be changed. Pts were assessed at mos 3 (n=59), 12 (n=58), and	At 24-mos f/u, 53 pts remained implanted; ratings were available for 42 of these pts. *Clinical outcomes at 24 mos (baseline, 24 mos, LOCF):* $HDRS_{28}$: 36.8, 20.2, 21.6 MADRS: 33.4, 19.9, 19.8 CGI-I: 4.1, 2.4, 2.4 GAF: 40.6, 62.6, 62.0 YMRS: 2.1, 1.4, 1.2 All 24-mo values significantly different from baseline, except YMRS.	Results suggest that some pts w/ tx-resistant depression may show long-term response to adjunctive VNS. *Limitations:* Lack of control or comparison grp; small sample size; concomitant medications could confound results; missing data w/ only 42/59 (71%) pts w/ full data set at 24 mos.

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Medical Center, Dallas, TX; New York State Psychiatric Institute; Physicians and Surgeons College of Columbia University, New York, NY Multicenter, nonrandomized, open-label, single-arm study – study extension (D01) (Rush et al., 2000; Sackeim et al., 2001a) *F/u:* 24 mos *Funding source:* Cyberonics Inc.	(47%); MDD single episode (27%); bipolar I disorder (10%); bipolar II disorder (17%)	24 (n=53). *Outcome measures:* $HDRS_{28}$, MADRS, YMRS, CGI-I, GAF, YMRS; remission defined as $HDRS_{28}$ score ≤10; response defined as ≥50% reduction from baseline $HDRS_{28}$ total score	Based on LOCF analysis, $HDRS_{28}$ response rate was 42% (25/59) after 2 yrs of adjunctive VNS; remission rate was 22% (13/59). At 24 mos, there were 2 deaths (unrelated to VNS), 4 w/drawals, 81% still receiving VNS. *Complications:* 40 serious adverse events occurred during the 24-mo f/u and included: suicide attempts (3); worsened depression (10); dysphoria (1); manic episode (2); agitation (1); CNS toxicity (1).	*Quality:* Poor
Rush, Sackeim et al. (2005)* 21 VNS study centers in U.S. and Canada Open-label extension of D02 study (see Rush et al., 2005a) *F/u:* 1 yr *Funding source:* Cyberonics Inc.	n=205 pts who completed acute phase of D02 study (mean age 46.3 yrs; 63.9% female; 96.6% Caucasian) *Inclusion criteria:* See Rush, Marangell et al. (2005) *Exclusion criteria:* See Rush, Marangell et al. (2005) *Clinical hx:* Unipolar 90.2%; bipolar 9.8%	Pts received a total of 12 mos of active VNS. During this open-label extension phase, medications could be changed in type or dose and ECT could be provided, and VNS parameters could also be changed. Outcomes were assessed at mos 3 (n=205), 6 (n=197), 9 (n=186), and 12 (n=181).	Clinical outcomes (mean, baseline; 12 mos observed; 12 mos LOCF): $HRSD_{24}$: 28.0; 19.6; 20.6 MADRS: 30.8; 21.2; 22.2) $IDS\text{-}SD_{30}$: 42.9; 32.6; 33.6 All measures $P<0.001$ comparing baseline, 12 mos observed, and 12 mos LOCF. At 12 mos, $HRSD_{24}$ response rate was 27.2% (55/202); remission rate was 15.8% (32/202). MADRS response rate was 28.2% (57/202); $IDS\text{-}SD_{30}$ response rate was 34% (68/200). *Complications:* See Rush et al. (2005a) for adverse events during acute phase of study (1st 10 wks of VNS tx). During extension study period, 24 pts discontinued tx, 7 for adverse	Results suggest that long-term VNS may improve symptoms in some pts w/ tx-resistant depression, when used as an adjunct to medications and/or ECT. *Limitations:* Concomitant txs varied among pts, confounds interpretation of VNS tx effect; data missing w/ only 177 pts w/ complete data sets. *Quality:* Fair (upgraded from poor based on large sample size, well defined pt

Authors/Study Design	Study Population	Treatment Protocol	Results	Conclusions/Limitations/ Quality Ratings
		Outcome measures: $HDRS_{28}$ Response Rate and % Improvement from Baseline, MADRS Response Rate and % Improvement from Baseline, CGI-I Response Rate, IDS-SR_{20} Response Rate and % Improvement from Baseline, MOS SF-36. Remission defined as score ≤9 on $HDRS_{24}$, ≤14 for IDS-SR_{30}, or ≤10 on MADRS; response defined as ≥ 50% reduction from baseline $HDRS_{24}$, IDS-SR_{30}, or MADRS score, or CGI-I of 1 or 2.	events, 17 for lack of efficacy or other reasons. Serious adverse events included worsening depression, hospitalizations; less serious events most frequently reported included headache, neck pain, pain, dysphagia, dyspnea, cough, and voice alteration.	selection criteria, extension study of original RCT)
Corcoran et al. (2006) Beaumont Hospital, Dublin, Ireland Prospective, open-label, single-arm study to evaluate VNS for tx-resistant depression *F/u:* 12 mos *Funding source:* Cyberonics Inc.	n=11 pts (mean age 43 yrs; 73% women, 27% men) *Inclusion criteria:* Pts w/ chronic MDD, current episode>2 yrs; ≥20 on HDRS scale; failed to respond to ≥2 different medication trials *Exclusion criteria:* NR *Clinical hx (%pts):* Mean length of depression was 20±8.34 yrs; previous ECT (55%)	Responders defined as improvement in $HDRS_{24}$ ≥50%. *Outcome measures:* Changes in depression severity assessed w/ $HDRS_{24}$, MADRS, and IDS-SR; complications	Changes in depression severity at baseline, 3 mos, and 12 mos (points±SD): $HDRS_{24}$: 36.36±3.44; 28.27±8.52; 19.27±12.74 (*P*=0.001) MADRS: 39.45±5.43; 30.55±10.50; 24.27±13.09 (*P*=0.013) IDS-SR: 57.81±8.44; 43.73±13.53; 31.81±19.41 (*P*=0.002) 1 responder at 3 mos, 2 at 6 mos, and 6 at 12 mos. *Complications (# pts):* Suicide (1), pulmonary emboli (1), vocal palsies (2).	Results suggest that VNS improves depression in pts w/ tx-resistant MDD. However, the study was uncontrolled and a placebo effect cannot be excluded. *Limitations:* Very small sample size, lack of control and rater blinding. *Quality:* Poor
Sackeim, Brannan, Rush, George, Marangell, & Allen (2007)*†	n=264 pts D01: n=59 pts (mean age 46.7 yrs; 35.6% men, 64.4% women)	See Rush et al. (2005a) and Sackeim et al. (2001a). Pts assessed at baseline,	In D01 study, 30.5% were early responders, 23.7% were late responders, and 45.8% of pts did not respond to VNS. Whereas in the D02 studies, 14.6%, 19.5%, and 65.9% of pts were early, late, and nonresponders, respectively.	Results indicate that pts who respond to VNS maintain tx benefit for up to 2 yrs in early responders, and up to 1 yr in late

Authors/Study Design	Study Population	Treatment Protocol	Results	Conclusions/Limitations/ Quality Ratings
21 VNS study centers in U.S. and Canada Analysis of long-term results of D01 and D02 studies (see Rush, Marangell et al., 2005a; Rush, Sackeim et al., 2005b) *F/u:* 2 yrs *Funding source:* Cyberonics Inc.	D02: n=205 pts (mean age 46.3 yrs; 36.1% men, 63.9% women) *Inclusion criteria:* See Rush, Marangell et al. (2005) and Sackeim, Rush et al., (2001**)**; ≤6 adequate tx trials in current episode; $HDRS_{24}$ score ≥18 at study entry *Exclusion criteria:* See Rush, Marangell et al. (2005) and Sackeim, Rush et al., (2001) *Clinical hx:* See Rush, Marangell et al. (2005), Sackeim, Rush et al., (2001)	3-mos intervals for 24 mos. Responders had ≥50% reduction in $HDRS_{24}$ scores at 3 mos; late responders met this criterion at 12 mos but not at 3 mos. For long-term f/u, the level was decreased to 40%. *Outcome measures:* Improvements of depression ($HDRS_{24}$, BDI-II, IDS-SR); % pts maintaining tx response at 12 and 24 mos	In D02 study, 19/30 pts (63.3%) who were early responders maintained tx benefit at 12 mos; 23/30 pts (76.7%) were still responders at 24 mos. The study noted 40 late responders; of these, 26 pts (65.0%) were still responders at 24 mos. In D01 study, 13/18 pts (72.2%) who were early responders maintained tx benefit at 12 mos; 11/18 pts (61.1%) were still responders at 24 mos. Among later responders 11/14 pts (78.8%) maintained tx benefit until 24 mos. *Mean improvements over entire study period for D01 and D02, respectively (%mean improvement):* Early responders: 61.6%±20.6%; 54.7±16.1% Late responders: 60.8±21.4%; 51.3±20.5% Nonresponders: 24.5±18.8%; 12.9±19.0% Differences among grps were statistically significant (*P*<0.0001 for both, D01 and D02 comparisons). In early responders, mean % improvements in $HDRS_{24}$ scores were 66.4% at 3 mos; and ranged from 51.8% to 59.8% at 9 to 24 mos. Late responders experienced a mean 66.4% improvement at 12 mos; and 45.4% to 49.8% at 18 to 24 mos. In nonresponders, improvements ranged from 3.4% at 3 mos to 19.0% at 21 mos. *Complications:* NR	responders. There is a difference in mean change in $HDRS_{24}$ scores among responders and nonresponders. *Limitations:* Lack of control grp for D01 study and long-term f/u in D02; small sample sizes for long term-fu comparisons, statistical validity of intergrp comparison NR; for long-term f/u, response rate was defined as 40% improvement rather than 50% improvement in $HDRS_{24}$ scores. *Quality:* Fair (upgraded from poor based on large sample size, well defined pt selection criteria, extension study of original RCT)
Marangell et al. (2008) 2 centers in the U.S. Prospective, open-label, single-	n=9 pts (mean age 46.9 yrs, range 23-57; 2 men, 7 women) *Inclusion criteria:* Pts w/ ongoing manic, hypomanic, or depressive symptoms	Pts underwent 8-wk baseline period. Pts had to be on stable psychotropic medication ≥4 wks prior to baseline assessment. Following NCP implantation was a 2-wk	Originally, 10 pts received the NCP device. Of these, 2 pts did not complete the 40-wk protocol, of which 1 pt was noncompliant w/ protocol and 1 pt committed suicide. NIMH LCM-p outcomes presented as mean baseline score ± SD (points), mean	Results of this small pilot study suggest that VNS may improve symptoms of depression and function in pts w/ rapid cycling bipolar disorder. However, 1 measure of depression

Authors/Study Design	Study Population	Treatment Protocol	Results	Conclusions/Limitations/ Quality Ratings
arm, pilot study to evaluate VNS for rapid cycling bipolar disorder (possibly D06 study) *F/u:* 12 mos *Time frame:* June 2001 – July 2005 *Funding source:* Cyberonics Inc.	>50% of the time during an 8-wk baseline assessment period; concomitant psychotropic medication was permitted *Exclusion criteria:* NR *Clinical hx (#pts):* Bipolar disorder I (7), bipolar disorder II (2)	recovery period w/o stim (stim-off). This was followed by 2-wk adjustment of stim parameters. For the following 40 wks of tx, pts were assessed every 2 wks and stim parameters changed if necessary. *Outcome measures:* Symptoms severity assessed by NIMH LCM-p (primary); changes in symptoms of depression ($HDRS_{28}$, $HDRS_{24}$, $IDS\text{-}SR_{30}$); symptoms of mania and hypermania (YMRS); CGI; psychological, social, and occupational function (GAF) (secondary)	improvement from baseline ± SD (points); mean %improvement: Total illness: 2.08±0.61; 0.79±0.73 (*P*=0.012); 38.1% Depression symptoms: 1.83±0.82; 0.69±0.72 (*P*=0.021); 37.9% Mania symptoms: 0.25±0.25; 0.10±0.17 (NS); 40.2% Secondary clinical outcomes presented as baseline score ± SD (points), mean absolute improvement ± SD (points); mean %improvement from baseline: $HDRS_{24}$: 20.9±7.2; 7.1±9.5; 27.3% YMRS: 7.4±8.2; 4.2±5.0; -18.5% (NS for %change) MADRS: 22.6±5.9; 9.2±9.7; 38.3% CGI: 4.2±0.7; 1.0±1.3; 20.6% $IDS\text{-}SR_{30}$: 33.1±10.7; 7.9±14.8; 17.3% (NS for absolute and % change) GAF: 55.1±6.2; 10.7±8.7; 21.4% All comparisons statistically significant except $IDS\text{-}SR_{30}$; and YMRS for %improvement. *Complications:* >2 pts experienced hoarseness, postop pain/burning at device site, voice change w/ stim, shortness of breath. 1 pt committed suicide. This was judged to be unrelated to VNS. No other serious complications occurred.	($IDS\text{-}SR_{30}$) did not improve during the study; episodes of mania or hypermania might not be improved. Sample size may have been too small to detect improvements on all scales. Furthermore, this was an uncontrolled study and the actual tx benefit might be smaller than reported. *Limitations:* Very small sample size; lack of control and lack of blinding; concomitant use of psychotropic medication. *Quality:* Poor NOTE: 2 of 10 pts who underwent device implantation were not evaluable. However, the authors state that 9 pts were evaluated.
Schlaepfer et al. (2008) Multiple medical centers in 6 European countries D03 study: Open-label, uncontrolled study to evaluate	n=74 pts (mean 47.4 yrs; 32.4% men, 67.6% women) *Inclusion criteria:* Age 18-80 yrs; on-psychotic MDD or bipolar I or II disorder; duration of current MDE >2 yrs and/or >4 lifetime MDEs; score ≥20 on $HRSD_{24}$; # failed adequate	Baseline assessment for up to 4 wks. Pts w/ $HRSD_{24}$ score ≥20 underwent NCP implantation. Following implantation, pts underwent 2-wk single-blind period (stim-on, stim-off). Devices were turned	Of 74 pts, 4 withdrew consent, 7 pts discontinued study during 1st yr of f/u; of these, 2 had committed suicide. Response rates at 3, 6, 9, 12 mos (% pts): Observed cases: 36%, 44%, 53%, 55% LOCF: 34%, 39%, 46%, 47% These decreases, for both types of analysis, were statistically significant (*P*=0.000 for both).	Results suggest that long-term VNS may improve symptoms in some pts w/ tx-resistant depression. *Limitations:* Lack of control grp; unblinded data analysis; some pts received concomitant antidepressant tx, which may have

Authors/Study Design	Study Population	Treatment Protocol	Results	Conclusions/Limitations/ Quality Ratings
VNS as an adjunct to pharmacotx for depression *F/u:* 12 mos *Time frame:* 2001-2005 *Funding source:* Cyberonics Inc.	medication trials ≥2 but <6 txs; pts w/ bipolar disorder had to be either tx resistant, intolerant to, or have medical contraindication to lithium; inadequate clinical improvement during ≥6 wks psychotherapy during any MDE; concomitant antidepressant tx permitted if stable for 4 wks prior to study *Exclusion criteria:* Pts w/ atypical or psychotic depression; hx of schizophrenia, schizoaffective disorder or delusional disorder; amnesic or other cognitive disorder; clinically significant, current suicidal ideation; health risks related to surgical procedure and VNS stim; pregnant women and those not using adequate birth control *Clinical hx (%pts):* Unipolar recurrent (55.4%); unipolar, single episode (17.5%); bipolar I (12.2%); bipolar II (14.9%); total unipolar (73%)	on if pts scored ≥18 on $HRSD_{24}$ scale at end of 2 wks. In the following 2 wks, stim was adjusted to maximum comfortable level; stim parameters were kept stable during following 8 wks (acute phase). Long-term f/u followed acute phase. Pts assessed at 1, 2, 3, 4, 6, and 8 wks during acute phase. If criteria for response was met (≥50% reduction in $HRSD_{24}$ scores) pts were evaluated every mo for 9 mos. *Outcome measures:* ≥50% reduction in $HRSD_{24}$ scores from baseline, remission defined as $HRSD_{24}$ score ≤10 (primary); MADRS, IDS-SR; complications, including presence of mania (YMRS scale) (secondary)	Secondary outcomes: Reduction in depression severity by MADRS and IDS-SR were also statistically significant. *Complications (% events):* Acute: Voice alteration (63%); cough (26%); pain (20%); dyspnea (10%). At 1-yr f/u: Voice alterations (55%); dyspnea (10%). Serious complications resulting in hospitalization (# episodes): Worsening of depression (7); suicide (2); brain hemorrhage due to suicide attempt (1); nephrolithiasis (1); cholelithiasis (1); pulmonary embolism (1); mania (1); syncope (1). NOTE: The investigators judged only the manic episode as related to VNS.	confounded results. *Quality:* Poor

* Study populations overlap
† Study populations overlap

GUIDELINES

All MED core sources were searched for health technology assessments (HTAs) and guidelines. In addition, practice guidelines and HTAs were searched for the American Psychiatric Association and the California Technology Assessment Forum. Guidelines published after 2004 were included. The search identified the following guidelines:

Blue Cross Blue Shield (BCBS)

BCBS published guidelines regarding VNS for treatment-resistant depression in 2005 and 2006. These guidelines are archived and are no longer available on the BCBS website (BCBS, 2006).

California Technology Assessment Forum (CTAF)

The CTAF published an HTA in February 2006 (CTAF, 2006). CTAF reviews technologies with regard to five criteria that have to be met: (1) the technology must have FDA approval; (2) the scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes; (3) the technology must improve the net health outcomes; (4) the technology must be as beneficial as any established alternatives; and (5) the improvement must be attainable outside the investigational settings. CTAF concluded that VNS for depression does not meet criteria four and five for effectiveness and improvement of health outcomes in treatment-resistant depression.

Institute for Clinical Systems Improvement (ICSI)

ICSI published a guideline for major depression in adults in primary care (ICSI, 2009) and concluded that, although VNS is approved by the FDA for treatment-resistant depression, due to the lack of double-blind controlled studies and the inconclusive result in the one available study (Rush, Marangell et al., 2005), the quality of the evidence currently does not meet ICSI's threshold for recommendation.

Kaiser Permanente Care Management Institute (KPCMI)

The Kaiser Permanente Care Management Institute published an update to their guideline in March 2006, concluding that for patients with mild to moderate Major Depressive Disorder (MDD) whose symptoms fail to remit after adhering to first-line treatment, there is insufficient evidence to recommend vagus nerve stimulation (KPCMI, 2006).

NICE is in the process of writing an HTA on VNS for treatment-resistant depression (NICE, 2009). The anticipated publication date is in the summer of 2009.

ECONOMIC EVALUATIONS

A search of the peer-reviewed medical literature identified two economic evaluations for VNS in depression (Cohen & Allen, 2008; Sperling et al., 2009). However, when efficacy has not been proven, economic evaluations cannot substantiate cost-effectiveness.

Cohen & Allen (2008) performed the first study, comparing the costs of VNS as an adjunct to standard treatment versus standard treatment alone from a payer perspective. Cyberonics Inc. participated and paid for this study. The Medstat Group's MarketScan Research Database and the Medicare database served as a source of healthcare utilization and claims data. Results from the D01 and D02 study formed the basis for the outcomes data. The MarketScan database contained 483 patients with major treatment-resistant depression. Also included were 7335 patients with nonresistant major depression. This group provided data on hospitalization costs not directly related to treatment-resistant depression. The authors calculated that in treatment resistant depression, the annual costs for the treatment of patients who do not receive VNS are $40,326 for hospitalization alone and $46,567 for inpatient and outpatient treatment combined. Device and implantation costs were estimated to be $28,396. The authors used two scenarios to calculate potential savings and the respective time frame in which the costs for the device would have been recuperated: a moderate and an optimistic cost-reduction scenario.

Based on the MarketScan and pooled outcomes data, the savings related to the use of VNS were $2974 at 5 years of device life and $23,539 at 8 years for the moderate scenario. For the optimistic scenario, cost savings were $12,914 at 5 years and $40,935 at 8 years. For the moderate scenario, the device costs would have been recuperated at 4.57 years and at 3.62 years for the optimistic scenario. Based on the Medicare and pooled outcomes data, the potential savings in the moderate scenario were $8358 at 5 years and $32,385 at 8 years. The respective values for the optimistic scenario were $19,837 at 5 years and $52,473 at 8 years. The resulting break-even device life was 3.96 years for the moderate scenario and 3.18 years for the optimistic scenario. The range for the break-even device lifetime was 2.3 to 5.7 years.

In a second economic evaluation, Sperling, Reulbach, & Kornhuber (2009) evaluated the cost effectiveness of VNS for major depression in a prospective nonrandomized controlled study. The study enrolled nine patients receiving VNS (mean age 50 years; five women, four men) and nine patients receiving standard therapy (mean age 50 years; five women, four men). The study was conducted between 2002 and 2005 at the University Hospital in Erlangen (Germany). The $HDRS_{28}$ scale was the basis for the

psychopathological diagnosis. The mean $HDRS_{28}$ score was 23.7 points in the VNS group and decreased to 10.2 points at 12 months (P<0.001). There was no significant improvement in $HDRS_{28}$ scores in the control group. VNS significantly decreased the number of days hospitalized from a mean of 65 days prior to VNS to a mean of 44 days after 12 months of VNS. VNS also significantly decreased the number of psychiatric consultations from 33 to 14 visits per year. There was no change in these parameters for the control group. VNS also decreased medication use from a mean of 4.1 to a mean of 2.7 psychotropic drugs per day. Again, there was no significant change in the control group (3.4 and 3.8, respectively). In addition, VNS decreased the mean number of absent days in those patients who were still employed from 160 to 136 days per year.

This resulted in a cost reduction per year of 7350 Euros for hospital stays, 570 Euros for the reduction in psychiatric treatment, and 600 Euros for psychotropic medication. The authors estimated that the fewer days of work lost due to therapy resulted in an additional 1000 Euros savings to the German national economy. The combined savings would be 9250 Euros. The authors concluded that the use of VNS would not only ameliorate symptoms but that an amortization of cost is possible.

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APPENDIX I

MED PROJECT	Methodology Checklist: Systematic Reviews and Meta-analyses				
Study citation (*Include last name of first author, title, year of publication, journal title, pages*)					
MED Topic:		Key Question No.(s):			
Checklist completed by:			Date:		
Section 1: Internal validity					
In a well conducted systematic review		In this study the criterion is met:			
1.1	The study addresses an appropriate and clearly focused question.	YES	NO	UNCLEAR	N/A
1.2	An adequate description of the methodology used is included, and the methods used are appropriate to the question.	YES	NO	UNCLEAR	N/A
1.3	***The literature search is sufficiently rigorous to identify all the relevant studies.***	YES	NO	UNCLEAR	N/A
1.4	***The criteria used to select articles for inclusion is appropriate.***	YES	NO	UNCLEAR	N/A
1.5	Study quality is assessed and taken into account.	YES	NO	UNCLEAR	N/A
1.6	There are enough similarities between the studies selected to make combining them reasonable.	YES	NO	UNCLEAR	N/A
1.7	There is a conflict of interest statement.	YES	NO	UNCLEAR	N/A
1.8	There is a description of source(s) of funding.	YES	NO	UNCLEAR	N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY					
2.1	***How well was the study done to minimize bias?*** **Code: Good, Fair or Poor**	GOOD	FAIR	POOR	
2.2	If coded as fair or poor, what is the likely direction in which bias might affect the study results?				
2.3	Are the results of this study directly applicable to the patient group targeted by this key question?	YES	NO	UNCLEAR	N/A
2.4	Other reviewer comments:				

APPENDIX II

MED PROJECT	Methodology Checklist: Randomized Controlled Trials
Study identification (*Include author, title, year of publication, journal title, pages*)	
MED topic:	Key Question No(s):
Checklist completed by:	Date:

Section 1: Internal validity

	In a well conducted RCT study…	In this study this criterion is:
RANDOM ALLOCATION OF SUBJECTS		
1.1	An appropriate method of randomization was used to allocate participants to intervention groups.	YES NO UNCLEAR N/A
1.2	***An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.***	YES NO UNCLEAR N/A
1.3	The intervention and control groups are similar at the start of the trial. (The only difference between groups is the treatment under investigation.)	YES NO UNCLEAR N/A
ASSESSMENT AND FOLLOW-UP		
1.4	Investigators, participants, and clinicians were kept 'blind' about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	YES NO UNCLEAR N/A
1.5	The intervention and control groups received the same care apart from the intervention(s) studied.	YES NO UNCLEAR N/A
1.11	The study had an appropriate length of follow-up.	YES NO UNCLEAR N/A
1.12	All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up).	YES NO UNCLEAR N/A

1.14	What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did not complete the intervention(s)?	
1.15	*All the subjects were analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)*	YES NO UNCLEAR N/A

ASSESSMENT AND FOLLOW-UP, Cont.		
1.16	All relevant outcomes are measured in a standard, valid and reliable way.	YES NO UNCLEAR N/A
1.17	The study reported only on surrogate outcomes. (If so, please comment on the strength of the evidence associating the surrogate with the important clinical outcome for this topic.)	YES NO UNCLEAR N/A
1.18	The study uses a composite (vs. single) outcome as the primary outcome. If so, please comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.19	There is a conflict of interest statement.	YES NO UNCLEAR N/A
1.20	There is a description of source(s) of funding.	YES NO UNCLEAR N/A
Section 2: Overall Study Assessment		
2.1	***How well was the study done to minimize bias?*** **Code Good, Fair, or Poor**	GOOD FAIR POOR
2.2	If coded as Fair or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.7	Other reviewer comments:	

APPENDIX III

MED PROJECT	Methodology Checklist: Cohort Studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Review topic:	Key Question No.(s), if applicable:
Checklist completed by:	Date:

Section 1: Internal validity

	In a well conducted cohort study:	In this study the criterion is:
1.1	The study addresses an appropriate and clearly focused question.	YES NO UNCLEAR N/A
	SELECTION OF SUBJECTS	
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	YES NO UNCLEAR N/A
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	YES NO UNCLEAR N/A
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis.	YES NO UNCLEAR N/A
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	
1.6	**Comparison is made between full participants and those who dropped out or were lost to follow up, by exposure status.**	YES NO UNCLEAR N/A
	ASSESSMENT AND FOLLOW-UP	
1.7	The study employed a precise definition of outcome(s) appropriate to the key question(s).	YES NO UNCLEAR N/A
1.8	The assessment of outcome(s) is made blind to exposure status.	YES NO UNCLEAR N/A
1.9	Where outcome assessment blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	YES NO UNCLEAR N/A
1.10	The measure of assessment of exposure is reliable.	YES NO UNCLEAR N/A

1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	YES NO UNCLEAR N/A
1.12	Exposure level or prognostic factor is assessed more than once.	YES NO UNCLEAR N/A
1.13	The study had an appropriate length of follow-up.	YES NO UNCLEAR N/A
1.14	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	YES NO UNCLEAR N/A
CONFOUNDING		
1.15	The main potential confounders are identified and taken into account in the design and analysis.	YES NO UNCLEAR N/A
STATISTICAL ANALYSIS		
1.16	Have confidence intervals been provided?	YES NO UNCLEAR N/A
CONFLICT OF INTEREST		
1.17	There is a conflict of interest statement.	YES NO UNCLEAR N/A
1.18	There is a description of source(s) of funding.	YES NO UNCLEAR N/A
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimize the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code Good, Fair, or Poor*	GOOD FAIR POOR
2.2	If coded as Fair, or Poor what is the likely direction in which bias might affect the study results?	
2.3	Are the results of this study directly applicable to the patient group targeted by this topic?	YES NO UNCLEAR N/A
2.4	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	YES NO UNCLEAR N/A
2.5	Other reviewer comments:	

APPENDIX IV
Summary of D01 to D06 Studies for Vagus Nerve Stimulation

Key: FDA, Food and Drug Administration; f/u, follow-up; n, sample size; NR, not reported; pt(s), patient(s); RCT, randomized controlled trial; tx, treatment; VNS, vagus nerve stimulation

Trial/Study Design	n	Design	F/u	Status	Citations
D01 Efficacy and safety of VNS in tx-resistant depression	60	Prospective, nonrandomized, open-label, single-arm study	10 wks on VNS; 12 mos extension	Completed	Rush et al. (2000); Sackeim et al. (2001a); Sackeim et al. (2001b); Marangell et al. (2002); Nahas et al. (2005); FDA (2005b); Sackeim et al. (2007)
D02 Efficacy and safety of VNS in tx-resistant depression	235	Prospective, acute, double-blind, placebo-controlled RCT and long-term f/u	0 wks on VNS (RCT); 24 mos extension (unblinded phase)	Completed	Carpenter et al. (2004) (partial results); Rush et al. (2005a); Rush et al. (2005b); FDA (2005b); Sackeim et al. (2007); Nierenberg et al. (2008)
D03 Efficacy and safety of VNS in tx-resistant depression	47	Prospective, nonrandomized, open-label, uncontrolled study	12 mos	Completed	Schlaepfer et al. (2008); FDA (2005b)
D04 Long-term effectiveness of VNS vs standard of care	138	Prospective, nonrandomized, open-label, single-arm study	12 mos	Completed	George et al. (2005); FDA (2005b)
D05 Videotape assessment of D02 pts	235	See D02	12 mos	NR	Unpublished; FDA (2005b)
D06 Efficacy and safety of VNS in pts w/ rapid cycling bipolar disorder	11 (9 completed study)	Prospective, nonrandomized, open-label, single-arm study	40 wks	Completed	Possibly Marangell et al. (2008); FDA (2005b)